Nephrology and Hypertension

BOARD REVIEW + PRACTICE TEST

THIRD EDITION

Phuong-Chi T. Pham
Phuong-Thu T. Pham

Wolters Kluwer

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Preface

A practicing nephrologist is expected to have a firm grasp on a wide scope of potentially life-threatening electrolyte and acid-base disturbances, acquired and inherited kidney diseases, acute kidney injuries, complex chronic kidney disease–related metabolic, endocrinologic, skeletal/mineral, and cardiovascular complications, difficult-to-treat hypertension, kidney stones, all kidney replacement modalities including hemodialysis, peritoneal dialysis, home hemodialysis, continuous kidney replacement therapy, and kidney transplant, among many other topics. Mastering this broad spectrum of diseases can be a difficult task for practicing nephrologists, particularly for those working in hectic private settings.

We aimed to write this book as an abbreviated review for renal fellows and general nephrologists who have limited time to study for the nephrology board certifying examination or who simply wish to review and update their nephrology knowledge. The book content closely reflects the American Board of Internal Medicine (ABIM) blueprint outlined for the Nephrology Certification Examination.

In this third edition, we updated the latest clinical practice guidelines and included more tables and figures to better illustrate difficult concepts, simplify differential diagnoses, and consolidate management strategies for commonly encountered conditions. Additionally, we provide a 240-question ABIM board-style practice test in the eBook to solidify your knowledge and exam-taking skills.

Abbreviations

AA: aristolochic acid
AA: amyloid A
AAN: aristolochic acid nephropathy
AAV: ANCA-associated vasculitis
Ab: antibody
Ab–Ag: antibody-antigen
ABD: adynamic bone disease
ABG: arterial blood gas
ABMR: antibody-mediated rejection
ABPM: ambulatory BP measurement
AC: adenylyl cyclase
ACA: anterior communicating artery
ACC: American College of Cardiology
ACD: acid citrate dextrose
ACE: angiotensin-converting enzyme
ACEi: angiotensin-converting enzyme inhibitors
ACKD: acquired cystic kidney disease
ACP: alternative complement pathway
ACR: albumin-to-creatinine ratio
ACR: albumin-to-creatinine ratio
ACR: American College of Radiology
ACS: abdominal compartment syndrome
ACTH: adrenocorticotropin hormone
AD: autosomal dominant
ADAMTS 13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADH: antidiuretic hormone
ADHF: acute decompensated heart failure
ADPKD: autosomal dominant polycystic kidney disease
ADTKD: autosomal dominant tubulointerstitial kidney disease
AE: anion exchanger
AER: albumin excretion rate
AF: atrial fibrillation
AFLP: acute fatty liver of pregnancy

AG: anion gap
AG: aminoglycosides
Ag: antigen
AGE: advanced glycation end product
AGXT: alanine-glyoxylate aminotransferase
AH50: alternative complement pathway assay
AHA: American College of Cardiology/American Heart Association
AHA: American Heart Association
AHG: anti-human globulin
aHUS: atypical hemolytic uremic syndrome
AIN: acute interstitial nephritis
AIP: acute intermittent porphyria
AKA: alcohol ketoacidosis
AKD: acute kidney disease/disorder
AKI: acute kidney injury
AKIN: acute kidney injury network
AL: amyloid light chain
ALA: aminolevulinic acid
ALAD: aminolevulinic acid dehydratase
ALK: anaplastic lymphoma kinase
ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALT: alanine aminotransferase
ALTITUDE: Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
AMI: acute myocardial infarction
AML: angiomyolipoma
AML: acute myeloid leukemia
AMR: antibody-mediated rejection
ANA: antinuclear antibody
ANCA: antineutrophil cytoplasmic autoantibody
ANP: atrial natriuretic peptide
anti-PLA2R: anti-phospholipase A2 receptor antibody
AOBP: automatic oscillometric BP
APC: antigen-presenting cells
APKD: autosomal dominant polycystic kidney disease
aPLs: antiphospholipid antibodies
APOL: apolipoprotein 1
APP: abdominal perfusion pressure
APRT: adenine phosphoribosyltransferase
APS: antiphospholipid syndrome
AQP1: aquaporin 1
AR: autosomal recessive

ARB: angiotensin receptor blocker
ARDS: acute respiratory distress syndrome
ARN: anticoagulant-related nephropathy
ARNi: ARB-neprilysin inhibitor
ARR: aldosterone to renin ratio
ART: antiretroviral
ASCVD: atherosclerotic cardiovascular disease
ASD: aldosterone synthase deficiency
ASDN: aldosterone sensitive distal nephron
ASO: antistreptolysin O
AST: American Society of Transplantation
AST: aspartate aminotransferase
AST: American Society of Transplantation
AT1R: angiotensin II type 1 receptor
ATG: antithymocyte globulin
ATI: acute tubular injury
ATIN: acute tubulointerstitial nephritis
ATN: acute tubular necrosis
ATP: adenosine triphosphate
ATTR: amyloid transthyretin
AUC: area under the curve
AURORA: A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis
AV: arteriovenous
AVF: arteriovenous fistula
AVG: arteriovenous graft
AVN: avascular necrosis
AVP: arginine vasopressin
AVP2R: arginine vasopressin 2 receptor
AVR: vasopressin receptor
AVS: adrenal venous sampling
AZA: azathioprine
BAFF: B-cell–activating factor
BAP: bone-specific alkaline phosphatase
BCC: basal cell carcinoma
BCG: Bacillus Calmette-Guérin
BCR-Abl: breakpoint cluster region, Abelson murine leukemia viral oncogene homolog
BCT: barbiturate coma therapy
BEN: Balkan endemic nephropathy
BES: balanced-electrolyte solutions
BHD: Birt-Hogg-Dube
BK: B-cell lymphoma kinase

BK: big-K^+
BKN: BK nephropathy
BKPyV: BK polyomavirus
BMD: bone marrow disorder
BMD: bone marrow density
BMI: body mass index
BP: blood pressure
BRAF: B-rapidly accelerated fibrosarcoma
BS: Bartter syndrome
BSA: body surface area
BSND: BS and sensorineural deafness
BUN: blood urea nitrogen
BVAS/WG: Birmingham vasculitis activity/Wegener granulomatosis score
BZP: *N*-benzylpiperazine
CA: carbonic anhydrase
CA-AKI: contrast-associated AKI
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CAH: congenital adrenal hyperplasia
CAKUT: congenital abnormality of the kidney and urinary tract
cAMP: cyclic adenosine monophosphate
c-ANCA: cytoplasmic-ANCA
CAPD: continuous ambulatory peritoneal dialysis
CAR: chimeric antigen receptor
cART: combined antiretroviral treatment
CaSR: calcium-sensing receptor
cBSA: cationic bovine serum albumin
CCB: calcium channel blocker
CCCR: calcium-to-creatinine clearance ratio
CCD: cortical collecting duct
CCM: cirrhotic cardiomyopathy
CDC: complement-dependent cytotoxicity
cDI: central diabetes insipidus
CDT: catheter-directed therapy
CEA: carotid endarterectomy
CFB: complement factor B
CFTR: cystic fibrosis transmembrane conductance regulator
CFU: colony-forming unit
CG: Cockcroft-Gault
CGM: continuous glucose monitoring
cGMP: cyclic guanosine monophosphate

CHD: coronary heart disease
CHF: congestive heart failure
CIN: chronic interstitial nephritis
CINAC: chronic interstitial nephritis in agricultural communities
CKD: chronic kidney disease
CKD-EPI: chronic kidney disease epidemiology collaboration
CKDi: cyclin-dependent kinase 4/6 inhibitor
CKDu: CKD of unknown cause
CKRT: continuous kidney replacement therapy
ClC: chloride channel
CLD: claudin
CLIA: Clinical Laboratory Improvement Amendments
CLL: chronic lymphocytic leukemia
CMS: Centers for Medicare & Medicaid Services
CMV: cytomegalovirus
CN: connecting segment
CNI: calcineurin inhibitor
CNS: central nervous system
CO: cardiac output
COLA: cysteine, ornithine, lysine, arginine
COPD: chronic obstructive pulmonary disease
$C_{OSM:}$ osmolar clearance
COX-2: cyclooxygenase-2
CPAP: continuous positive airway pressure
CPB: cardiopulmonary by pass
CPIs: checkpoint inhibitors
CPK: creatine phosphokinase
CPM: central pontine myelinolysis
CPP: cerebral perfusion pressure
cPRA: calculated panel reactive antibody
CR: complete remission
CRBSI: catheter-related bloodstream infection
CrCl: creatinine clearance
CRP: C-reactive protein
CRRT: continuous renal replacement therapy
CRS: cardiorenal syndrome
CSW: cerebral salt wasting
CT: computed tomography
CTA: computed tomogram angiography
CTDN: chlorthalidone
CTG: chronic transplant glomerulopathy

CTIN: chronic tubulointerstitial nephritis
CTLA-4: cytotoxic T-lymphocyte-associated antigen 4
CUL3: Cullin 3
CVA: cerebrovascular accident
CVC: central venous catheters
CVD: cardiovascular disease
CVP: central venous pressure
CVVH: continuous venovenous hemofiltration
CVVHDF: continuous venovenous hemodiafiltration
CYC: cyclophosphamide
D5: 5% dextrose
DAA: direct-acting antiviral
DART: diagnosing acute rejection in kidney transplant
DASH: dietary approaches to stop hypertension
DBP: diastolic blood pressure
DCIS: ductal carcinoma in situ
DCT: distal convoluted tubule
DDAVP: desmopressin
dd-cfDNA: donor-derived plasma cell-free DNA
DDD: dense deposit disease
DES: drug-eluting stent
DEXA: dual-energy x-ray absorptiometry
DGF: delayed graft function
DGKE: diacylglycerol kinase ξ
DHA: dihydroxyadenine
DHP: dihydropyridine
DI: diabetes insipidus
DIC: disseminated intravascular coagulation
DKD: diabetic kidney disease
DLBCL: diffuse large B-cell lymphoma
DM: diabetes mellitus
DNAJB9: DnaJ homolog subfamily B member 9
DNAJB9: DnaJ heat shock protein family member B9
DOAC: direct-acting oral anticoagulant
DOC: deoxycorticosterone
DOPA: dihydroxyphenylalanine
DOPPS: Dialysis Outcomes and Practice Patterns Study
DOX: doxazosin
DPP4: dipeptidyl peptidase-4
DR: diabetic retinopathy
DRESS: drug reaction with eosinophilia and systemic symptoms

DRI: direct renin inhibitor
dRTA: distal renal tubular acidosis
DSA: donor-specific antibody
dsDNA: double-stranded DNA
DST: dexamethasone suppression test
DTPA: diethylenetriaminepentaacetic acid
DTT: dithiothreitol
DVT: deep vein thrombosis
EA: efferent arteriole
EBNA1: Epstein-Barr nuclear antigen 1
EBV: Epstein-Barr virus
ECG: electrocar diogram
ECMO: extracorporeal membrane oxygenation
ECT: electron chain transport
EDTA: ethylenediaminetetraacetic acid
EF: ejection fraction
EFWC: electrolyte-free water clearance
EGF: epithelial growth factor
eGFR: estimated glomerular filtration rate
EGPA: eosinophilic granulomatosis with polyangiitis
EIA: enzyme immunoassay
ELAIN: Early Versus Late Initiation of Dialysis in Acute Kidney Injury trial
ELISA: enzyme-linked immunosorbent assay
EM: electron microscopy
ENaC: epithelial sodium channel
ENaCi: epithelial sodium channel inhibitor
EPO: erythropoietin
EPS: encapsulating peritoneal sclerosis
EPTS: estimated posttransplant survival
ER: endoplasmic reticulum
ERT: enzyme replacement therapy
ES: Endocrine Society
ESA: erythropoiesis-stimulating agent
ESKD: end-stage kidney disease
ESR: erythrocyte sedimentation rate
ESRD: end-stage renal disease
ESWL: extracorporeal shock-wave lithotripsy
ET: endothelin
ETAR: anti-endothelin-1 type A receptor
EVAR: endovascular aortic aneurysm repair

EVEREST: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan

FCP: fibrocystin/polyductin

FCXM: flow cytometry crossmatch

FDA: U.S. Food and Drug Administration

FDP: fibrinogen degradation product

$FeHCO_3$: fractional excretion of bicarbonate

FeMg: fractional excretion of magnesium

FeNa: fractional excretion of sodium

$FePO_4$: fractional excretion of phosphate

FeUrea: fractional excretion of urea

FF: filtration fraction

FFA: free fatty acid

FFP: fresh frozen plasma

FGF23: fibroblast growth factor 23

FH: familial hyperaldosteronism

FHH: familial hyperkalemic hypertension (Gordon) or familial hypocalciuric hypercalcemia

FIDELIO-DKD: Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease

FLC: free light chain

FMD: fibromuscular dysplasia

FMD: fibromuscular dystrophy

FMF: familial Mediterranean fever

FPE: foot process effacement

FSGS: focal segmental glomerulosclerosis

FST: furosemide stress test

FTA-ABS: fluorescent treponemal antibody absorption

FWC: free water clearance

FXM: flow crossmatch test

G6PD: glucose-6-phosphate dehydrogenase

GA: glutaminase

GAPDH: glyceraldehyde-3-phosphate dehydrogenase

GBM: glomerular basement membrane

GC: glucocorticoids

GCKD: glomerulocystic kidney disease

GCSF: granulocyte colony-stimulating factor

GDFT: goal-directed fluid therapy

GDMT: guideline-directed medical therapy

GFR: glomerular filtration rate

GH: growth hormone

GI: gastrointestinal

GLP-1 RA: glucagon-like peptide 1 receptor agonist
GN: glomerulonephropathy
GPA: granulomatosis polyangiitis
GRA: glucocorticoid remediable aldosteronism
GS: Gitelman syndrome
GU: genitourinary
H&E: hematoxylin and eosin
HAART: highly active antiretroviral therapy
Hb: hemoglobin
HbA1C: hemoglobin A1C
HBcAg: hepatitis B core antigen
HBeAg: hepatitis B e antigen
HbF: Higher fetal hemoglobin
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HbSC: sickle hemoglobin C
HbSS: homozygous for the β S allele
HbSβ: sickle β-thalassemia
HBV: hepatitis B virus
HC: hydroxychloroquine
HC: heavy chain
HCDD: heavy-chain deposition disease
HCG: human chorionic gonadotropin
HCST: hematopoietic stem cell transplant
HCT: hematopoietic cell transplantation
HCTZ: hydrochlorothiazide
HCV: hepatitis C virus
HD: hemodialysis
HDL: high-density lipoprotein
HDx: expanded hemodialysis
HELLP: hemolysis, elevated liver enzymes, low platelets
HF: heart failure
HFimpEF: HF improved ejection fraction
HFmrEF: HF with mildly reduced ejection fraction
HFpEF: HF with preserved ejection fraction
HFrEF: HF with reduced ejection fraction
HHD: home hemodialysis
HHRH: hereditary hypophosphatemia with rickets and hypercalciuria
HHV: human herpes virus
HIF-α: hypoxia-inducible factor-α
HITT: heparin-induced thrombocytopenia and thrombosis

HIV: human immunodeficiency virus
HIVAN: HIV-associated nephropathy
HIVICK: HIV-associated immune complex kidney disease
HLA: human leukocyte antigen
HNF: hepatic nuclear factor
HOPE: HIV Organ Policy Equity
HPF: high-power field
hPTH: hyperparathyroidism
HR: hazard ratio
HRE: hypoxia response element
HRS: hepatorenal syndrome
HSD: hydroxysteroid dehydrogenase
HSP: Henoch-Schönlein purpura
HSV: herpes simplex virus
HTN: hypertension
HUS: hemolytic uremic syndrome
HVHF: high volume hemofiltration
IAH: intra-abdominal hypertension
IAP: intra-abdominal pressure
IC: immune complex
IC: intercalated cell
ICD: implantable cardioverter-defibrillator
ICGN: immune complex glomerulonephritis
IC-MPGN: immune complex–mediated membranoproliferative glomerulonephritis
ICP: intracranial pressure
ICU: intensive care unit
IDEAL-ICU: Initiating Dialysis Early Versus Delayed in the Intensive Care Unit
IDH: isolated dominant hypomagnesemia
IDMS: isotope dilutional mass spectrometry
IDWG: interdialytic weight gain
IF: immunofluorescence
IgADIRGN: IgA-dominant infection-related GN
IgAN: immunoglobulin A nephropathy
IgAV: IgA vasculitis
IGF1: insulin-like growth factor
IGFBP7: insulin-like growth factor binding protein 7
IGT: impaired glucose tolerance
IHD: intermittent hemodialysis
IHD: ischemic heart disease
i-IFTA: interstitial inflammation in the areas of interstitial fibrosis and tubular atrophy
IJ: internal jugular

IL: interleukins
ILDA: independent living donor advo cate
iMGN: idiopathic membranous glomerulonephropathy
IMN: ischemic monomelic neuropathy
INDAP: indapamide
INF2: inverted formin-2
INH: isoniazid
INR: international normalized ratio
iPTH: intact parathyroid hormone
IRB: Institutional Review Board
IRIS: immune restoration inflammatory syndrome
ISH: isolated systolic hypertension
ISPD: International Society for Peritoneal Dialysis
IS-SHP: International Society for the Study of Hypertension in Pregnancy
IST: immunosuppressive therapy
IV: intravenous
IVC: inferior vena cava
IVF: intravenous fluid
IVIG: intravenous immunoglobulin
JC: John Cunningham
KATP: ATP-sensitive K^+ channels
KCTD1: potassium (K) channel tetramerization domain-containing 1 protein
KDIGO: Kidney Disease Improving Global Outcome
KDOQI: Kidney Disease Outcomes Quality Initiative
KDPI: Kidney Donor Profile Index
KIM-1: kidney injury molecule 1
KLHL3: Kelch-like 3
KPD: kidney-paired donation
KRT: kidney replacement therapy
KUB: kidney-ureter-bladder
LA: lactic acid
LAM: lymphangioleiomyomatosis
LC: light chain
LC n-3 PUFA: long chain omega-3 polyunsaturated fatty acid
LCDD: light-chain deposition disease
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
LDL-C: low-density lipoprotein cholesterol
LECT2: leukocyte chemotactic factor 2
LHCDD: light- and heavy-chain deposition disease
LI: lateralization index

LM: light microscopy
LMW: low-molecular-weight
LMWH: low-dose low-molecular-weight heparin
LN: lupus nephritis
LR: lactated ringer
LVEDA: left ventricular end-diastolic area
LVH: left ventricular hypertrophy
LVMI: left ventricular mass index
LVP: large-volume paracentesis
MAC: membrane-attack complex
MAGE-D2: melanoma-associated antigen D2
MAHA: microangiopathic hemolytic anemia
MALT: mucosa-associated lymphatic tissue
MAP: mean arterial pressure
MARS: molecular adsorbent recirculating system
MBD: mineral and bone disorder
MCD: minimal change disease
MCDK: multicystic dysplastic kidney disease
MCLN: mucocutaneous lymph node
MCO: medium cutoff
MCP: membrane cofactor protein
MCV: mean corpuscular volume
MDMA: 3,4-methylenedioxymethylamphetamine
MDRD: modification of diet in renal disease
MELD: model for end-stage liver disease
MEN: multiple endocrine neoplasia
MET: medical expulsion therapy
MFI: mean fluorescence intensity
MG: Michaelis-Gutmann
mGFR: measured GFR
MGUS: monoclonal gammopathy of undetermined significance
MHC: major histocompatibility complex
MI: myocardial infarction
MICB: MHC class I–related chain B
MIDD: monoclonal Ig deposition disease
MM: multiple myeloma
MMF: mycophenolate mofetil
MMR: measles, mumps, rubella
MN: membranous nephropathy
MODY5: maturity-onset diabetes of the young type 5
MONICA: Monitoring of Trends and Determinants in Cardiovascular Disease

MPA: microscopic polyangiitis
MPA: mycophenolic acid
MPAA: mycophenolic acid analogs
MPGN: membranoproliferative glomerulonephritis
MPO: myeloperoxidase
MRA: mineralocorticoid receptor antagonist
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
MRP: multidrug resistance-associated protein
MS: multiple sclerosis
MSK: medullary sponge kidney
mTOR: mammalian target of rapamycin
MTX: methotrexate
MUO: mixed uremic osteodystrophy
MVI: multivitamins
Na-Pi: sodium phosphate
NAT: nucleic acid testing
NBC: sodium bicarbonate cotransporter
NC: noncollagenous
NCC: sodium chloride cotransporter
nDI: nephrogenic diabetes insipidus
NE: norepinephrine
NEAD: never-ending altruistic donation
NELL1: neural epidermal growth factor-like 1
NEP: neutral endopeptidase
NFAT: nuclear factor of activated T-cell
NGAL: neutrophil gelatinase–associated lipocalin
NH_4^+: ammonium
NHANES: National Health and Nutrition Examination Survey
nHD: nocturnal HD
NHE: sodium-hydrogen exchanger
NHERF1: Na^+-H^+-exchanger regulatory factor 1
NKCC2: sodium-potassium 2 chloride cotransporter
NMDA: *N*-methyl-d-aspartate
NNRTI: nonnucleoside reverse transcriptase inhibitor
NNRTIs: nonnucleoside reverse transcriptase inhibitors
NODAT: new-onset diabetes after transplantation
NOS: not otherwise specified
NPHP: nephronophthisis
NPO: nil per os

NPT: sodium phosphate transporter
NRTI: nucleoside and nucleotide reverse transcriptase inhibitor
NRTIs: nucleoside reverse transcriptase inhibitors
NS: nephrotic syndrome
NS: normal saline
NSAIDs: nonsteroidal anti-inflammatory drugs
NSF: nephrogenic systemic fibrosis
NSIAD: nephrogenic syndrome of inappropriate antidiuresis
nsMRA: nonsteroidal mineralocorticoid receptor antagonist
NT-proBNP: N-terminal of the prohormone brain natriuretic peptide
NYHA: New York Heart Association
ODS: osmotic demyelination syndrome
OFC: osteitis fibrosa cystica
OGR1: ovarian cancer G-protein
OM: osteomalacia
OPTN: Organ Procurement Transplant Network
OSA: obstructive sleep apnea
OTC: over the counter
OXO: 5-oxoproline
P[K^+]: plasma potassium concentration
P[Na^+]: plasma sodium concentration
PA: primary aldosteronism
PA: pyroglutamic acid
PA: pulmonary artery
PAC: plasma aldosterone concentration
PAES: polyarylethersulfone
PAI-1: plasminogen activator–inhibiting factor 1
PAK: pancreas after kidney transplantation
PAN: polyarteritis nodosa
p-ANCA: perinuclear-ANCA
PaO_2: arterial partial pressure
PAoP: pulmonary arterial occlusion pressure
PARPi: poly-ADP ribose polymerase inhibitor
P_{ART}: arteriolar hydraulic pressure
PAS: periodic acid-Schiff
pATN: post-acute tubular necrosis
PBG: porphobilinogen
PBZ: phenoxybenzamine
PC: polycystin
PCI: percutaneous coronary intervention

PCR: polymerase chain reaction
PCR: protein-to-creatinine ratio
PCSK9: proprotein convertase subtilisin/kexin type 9
PCT: porphyria cutanea tarda
PCV: pneumococcal vaccine
PD: programmed death
PD: peritoneal dialysis
PDG: phosphate-dependent glutaminase
PDH: pyruvate dehydrogenase
PEEP: positive end-expiratory pressure
PEPCK: phosphoenolpyruvate carboxykinase
PET: peritoneal equilibrium testing
PG: prostaglandin
PG: propylene glycol
PGE2: prostaglandin E2
PGL: paraganglioma
PGNMID: proliferative glomerulonephritis with monoclonal immunoglobulin deposits
P-gp: P-glycoprotein
PH: primary hyperoxaluria
PHA: pseudohypoaldosteronism
PHD: prolyl hydroxylase domain enzyme
pHPT: primary hyperparathyroidism
pHTN: portal hypertension
PI: proteasome inhibitor
PICARD: Program to Improve Care in Acute Renal Disease
PICC: peripherally inserted central catheter
PIGN: postinfectious glomerulonephritis
PIKRT: prolonged intermittent renal replacement therapy
PJP: *Pneumocystis jirovecii pneumonia*
PKA: protein kinase A
PKD: polycystic kidney disease
PLA2R: phospholipase A2 receptor
PLCε1: phospholipase C epsilon 1
PLEX: plasma exchange
PlGF: placental growth factor
PMN: polymorphonuclear neutrophil
PNL: percutaneous nephrolithotomy
PO_4: phosphate
P_{OSM}: plasma osmolality
PP: pulse pressure
PPAR: peroxisome proliferator–activated receptor

PPARγ: peroxisome proliferator–activated receptor γ
PPD: purified protein derivative
PPGL: pheochromocytoma and paragangliomas
PPI: proton pump inhibitors
PPS: prospective payment system
PPSV23: pneumococcal polysaccharide vaccine
PPV: pulse pressure variation
PR: partial response
PR: partial remission
PR3: proteinase 3
PRA: plasma renin activity
PRA: panel of reactive antibody
PRES: posterior reversible encephalopathy syndrome
PRESERVE: Prevention of Acute Kidney Injury After Contrast Administration
ProPKD: Predicting Renal Outcome in Polycystic Kidney Disease
pRTA: proximal renal tubular acidosis
PSA: prostate-specific antigen
PSGN: poststreptococcal GN
PT: proximal tubules
PT/PTT: prothrombin time/partial thromboplastin time
PTA: pancreas transplantation alone
PTDM: posttransplantation diabetes mellitus
PTF: pentoxifylline
PTH: parathyroid hormone
PTHrP: parathyroid hormone–related peptides
PTLD: posttransplantation lymphoproliferative disorder
PTRA: percutaneous transluminal renal angioplasty
PTT: partial thromboplastin time
PTX: parathyroidectomy
$P_{US:}$ urinary space hydraulic pressure
pVHL: von Hippel-Lindau protein
QAPI: Quality Assessment and Performance Improvement
QNAT: quantitative nucleic acid testing
RAAS: renin-angiotensin-aldosterone system
RAI: renal angina index
RANKL: receptor activator of NF-kB Ligand
RASi: renin-angiotensin system inhibitor
RBC: red blood cell
RCA: regional citrate anticoagulation
RCC: renal cell carcinoma
RCT: randomized controlled trials

RCT: randomized placebo-controlled trial
RF: replacement fluid
RFR: renal functional reserve
RLS: restless leg syndrome
ROMK: renal outer medullary potassium channel
RPE: retroperitoneal fibrosis
RPGN: rapidly progressive glomerulonephritis
RR: relative risk
RRT: renal replacement therapy
RSV: respiratory syncytial virus
RTA: renal tubular acidosis
RTX: rituximab
RUA: routine urinalysis
RVT: renal vein thrombosis
S(PO_4): serum phosphate concentration
S[K^+]: serum potassium concentration
S[Na^+]: serum sodium concentration
SAG: serum anion gap
SAME: syndrome apparent mineralocorticoid excess
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SBP: systolic blood pressure
SBP: spontaneous bacterial peritonitis
SBW: standard body weight
SCa: serum calcium concentration
SCC: squamous cell carcinoma
SCD: sickle cell disease
SCN: sickle cell nephropathy
SCr: serum creatinine
SCT: sickle cell trait
SCUF: slow continuous ultrafiltration
$ScvO_2$: oxygen saturation in central vein
SCys: serum cystatin c
SEAS: Simvastatin and Ezetimibe in aortic stenosis
SEGA: subependymal giant-cell astrocytomas
sFLt1: soluble fms-like tyrosine kinase 1
SGLT2: sodium-glucose cotransporter-2
SGLT2i: sodium-glucose cotransporter-2 inhibitors
SHARP: Study of Heart and Renal Protection trial
SI: selectivity index
SIADH: syndrome of inappropriate antidiuretic hormone

SKA: starvation ketoacidosis
SLE: systemic lupus erythematosus
SLED: sustained low-efficiency dialysis
SLEDD: sustained low-efficiency daily dialysis
SLKT: simultaneous liver-kidney transplantation
SMART: Solutions and Major Adverse Renal Events Trial
SMg: serum magnesium concentration
SMP30: senescence marker protein-30
SNA: sympathetic nerve activity
SNAT: sodium-dependent amino acid transporter
SNS: sympathetic nervous system
SOG: serum osmolality gap
$S_{OSM:}$ serum osmolality
SPAK: Ste20-related proline alanine rich kinase
SPEB: streptococcal pyrogenic exotoxin B
SPK: simultaneous pancreas-kidney
SPRINT: Systolic blood PRessure INTervention trial
SPS: sodium polystyrene sulfonate
SRC: scleroderma renal crisis
SSA: sulfosalicylic acid
SSRI: selective serotonin reuptake inhibitor
STARRT-AKI: Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury
STEC: shiga toxin–producing enterohemorrhagic *Escherichia coli*
STS: sodium thiosulfates
SV: stroke volume
SVC: superior vena cava
SVR: systemic vascular resistance
SVV: stroke volume variation
t½: half-life
TAF: tenofovir alafenamide
TALH: thick ascending limb of Henle loop
TB: tuberculosis
TBM: tubular basement membrane
TBMN: thin basement membrane nephropathy
TBW: total body weight
TCA: tricarboxylic acid
TCMR: T-cell-mediated rejection
TCR: T-cell receptor
TDF: tenofovir disoproxil fumarate
TE: thromboembolism

TEB: thoracic electrical bioimpedance
TG: transplant glomerulopathy
TG: triglycerides
TGF: tubuloglomerular feedback
TGF: transforming growth factor
TGF-β: tumor growth factor-β
THBD: thrombomodulin
THDS7A: thrombospondin domain-containing 7A
THF: tetrahydrofolate
THSD7A: thrombospondin type 1 domain-containing 7A antigen
TIMP-2: tissue inhibitor of metalloproteinase-2
TINU: tubulointerstitial nephritis and uveitis
TIPS: transjugular intrahepatic portosystemic shunt
TKIs: tyrosine kinase inhibitors
TKV: total kidney volume
TLS: tumor lysis syndrome
TMA: thrombotic microangiopathy
TMP: transmembrane pressure
TMP-SMX: trimethoprim-sulfamethoxazole
TNF: tumor necrosis factor
tPA: tissue plasminogen activator
TPN: total parenteral nutrition
TRALI: transfusion-related acute lung injury
TRIM: transfusion-related immunomodulation
TRP: tubular reabsorption of phosphate
TRPM6: transient receptor potential melastatin channel 6
TRPV5: transient receptor potential cation channel subfamily V
TSAT: serum transferrin saturation
TSC: tuberous sclerosis complex
TSH: thyroid-stimulating hormone
TTP: thrombotic thrombocytopenic purpura
TZD: thiazolidinedione
U[K^+]: urine potassium concentration
U[Na^+]: urine sodium concentration
Ub: ubiquitin
UCr: urine creatinine
UF: ultrafiltration
UFH: unfractionated heparin
$U_{GLUCOSE:}$ urine glucose concentration
ULN: upper limit of normal

UMg: urine magnesium concentration
$U_{Na:}$ urine sodium
UNOS: United Network for Organ Sharing
UNOS MELD: United Network for Organ Sharing Model for End-Stage Liver Disease
UO: urine output
UOG: urine osmolality gap
$U_{OSM:}$ urine osmolality
uPCR: urine protein-to-creatinine ratio
UPN: uremic polyneuropathy
U_{PO4}: urine phosphate concentration
URR: urea reduction ratio
URS: ureteroscopy
USPSTF: U.S. Preventive Services Task Force
USRDS: United States Renal Data System
UT: urea transporter
UTI: urinary tract infection
$U_{UREA:}$ urine urea concentration
UV: urine volume
VA NEPHRON-D: Veterans Affairs Nephropathy in Diabetes trial
VBG: venous blood gas
VCA: viral capsid antigen
VCUG: voiding cystourethrogram
VDR: vitamin D receptor
VDRA: vitamin D receptor agonist
VDRL: Venereal Disease Research Laboratory
VEGF: vascular endothelial growth factor
VHL: von Hippel-Lindau
VHLp: von Hippel-Lindau protein
VKA: vitamin K antagonist
VLDL: very low-density lipoprotein
vWF: von Willebrand factor
VZV: varicella zoster virus
WBC: white blood cell
WCH: white coat hypertension
WHO: World Health Organization
WNK: with-no-lysine kinase
WRN: warfarin-related nephropathy
XLH: X-linked hypophosphatemia
XO: xanthine oxidase

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In honor and memory of our most loving and supportive parents, we direct all proceeds from this book to the Pham Family Patient Assistance Fund, created in September 2015, to help financially challenged patients pay for basic fees while seeking medical care.

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CHAPTER 1

Sodium and Water Abnormalities

Phuong-Chi T. Pham, Phuong-Mai T. Pham, Phuong-Anh T. Pham, Son V. Pham, and Phuong-Thu T. Pham

HYPONATREMIA

Definition

Hyponatremia is clinically defined as having measured serum sodium concentration ($S[Na^+]$) less than 136 mmol/L.

Determinants of Body Tonicity and Plasma Sodium Concentration ($P[Na^+]$)

Thirst

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH)

- AVP (ADH) is synthesized in paraventricular neurons of the hypothalamus as pre-pro-AVP and proteolytically cleaved into ***vasopressin*** + neurophysin II + ***copeptin*** (**Figure 1.1**). Because copeptin is a more stable peptide than ADH and can be easily measured, it can be used as a surrogate for ADH. Copeptin has been shown to parallel ADH levels in multiple clinical settings:

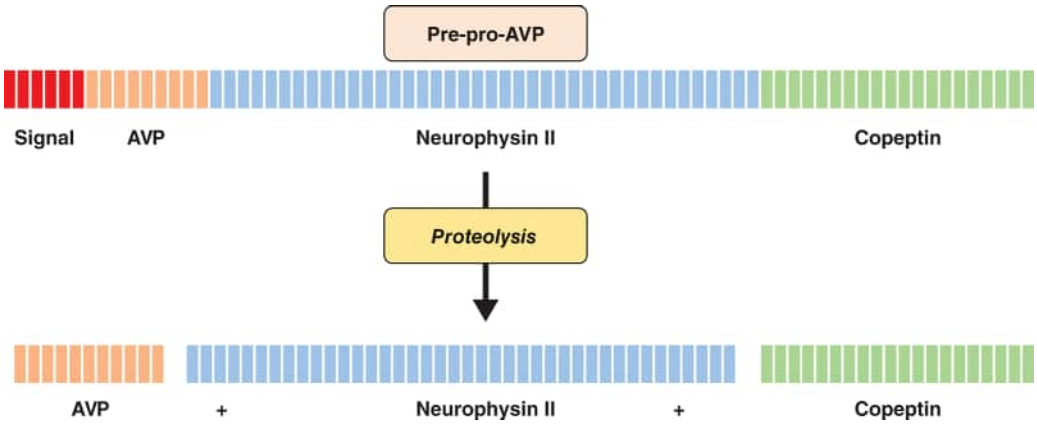


FIGURE 1.1 **Proteolysis of pre-pro-vasopressin.** Arginine vasopressin (AVP, also known as antidiuretic hormone [ADH]) is synthesized in paraventricular neurons of the hypothalamus as pre-pro-AVP and proteolytically cleaved into vasopressin + neurophysin II + copeptin.

Abbreviations: cDI, central diabetes insipidus; nDI, nephrogenic diabetes insipidus.

  - Similar to ADH, copeptin is increased in syndrome of inappropriate antidiuretic hormone (SIADH), nephrogenic diabetes insipidus (nDI), heart failure (HF), acute myocardial infarction, and sepsis.
  - Copeptin level is reduced in central diabetes insipidus (cDI).
- ADH is stored in secretory granules in the posterior pituitary and released upon osmotic (eg, hyperosmolality), hypovolemic, and nonosmotic/nonvolemic stimuli (eg, stress, drug induced, nausea, vomiting, pain).
- ADH may be seen as a "pituitary bright spot" or hyperintense T1 signal within the posterior pituitary on brain magnetic resonance imaging (MRI).
- MRI findings suggestive of absence of ADH or cDI include:
  - Loss of "pituitary bright spot"
  - Thickening or enlargement of pituitary stalk
  - One-third of patients with cDI may have normal brain MRI.

Presence of effective, exchangeable solutes Na^+ and K^+

- The early Edelman equation predicts that plasma sodium concentration $P[Na^+]$ is directly proportional to $(Na^+_e + K^+_e)$:

$$P[Na^+] = 1.11 \times (Na^+_e + K^+_e)/(\text{total body water}) - 25.6$$

where (Na^+_e + K^+_e) represents the sum of total body *exchangeable* Na^+ and K^+ and the *constant 25.6* represents the pool of *osmotically inactive* Na^+ and K^+ (*eg, "inexchangeable" Na^+ and K^+ sequestered in bones, nonfluid phase*).

- Over the years, many modifications to the Edelman equation have been made, partly because the 1:1 equivalence of Na^+ and K^+ has been questioned. Modified equations may be more factually accurate but too complex to use in the clinical setting.
- Key point to remember from the Edelman equation for routine clinical purposes:

Equimolar amounts of exchangeable Na^+ and K^+ have similar effects on raising *P*[Na^+]. That is, administering 100 mmol of Na^+ increases *P*[Na^+] similarly as administering 100 mmol of K^+. **Figure 1.2** illustrates plausible mechanisms.

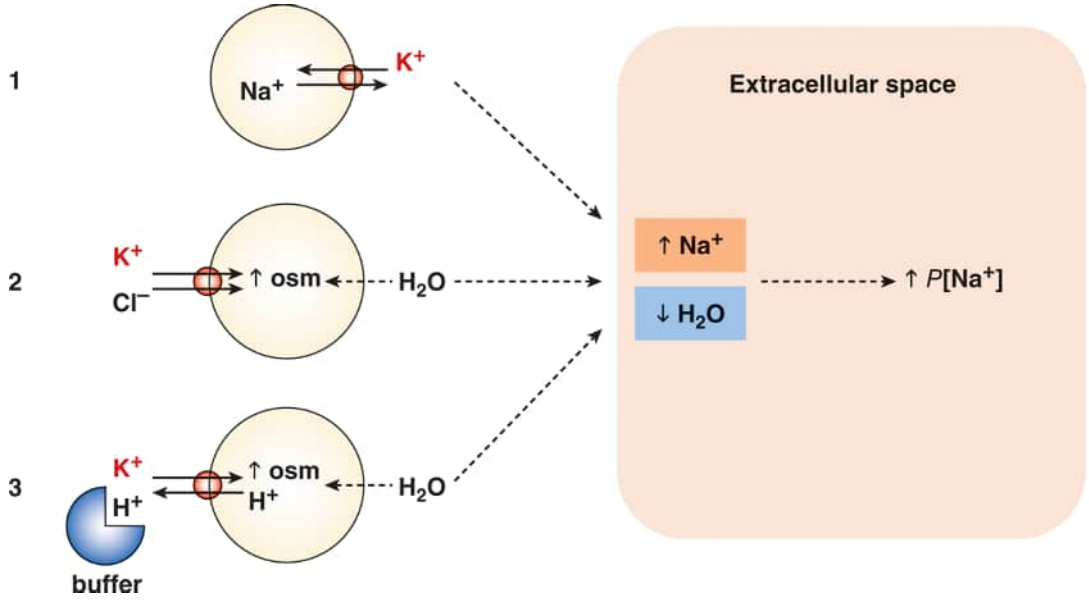


FIGURE 1.2 Mechanisms whereby potassium administration can increase plasma sodium concentration (*P*[Na^+]). 1. Potassium enters cells in exchange for sodium which increases *P*[Na^+]. 2. Potassium enters cells along with chloride to maintain electrical neutrality, which leads to increased intracellular osmolality and subsequent intracellular water shift. The reduced extracellular water volume leads to increased *P*[Na^+]. 3. Potassium enters cells in exchange for a proton. While potassium entry increases intracellular osmolality, leading to intracellular water shift and subsequent increase in *P*[Na^+], the extracellular proton shift is taken up by the extracellular buffer system and does not affect extracellular osmolality.

Abbreviations: osm, osmolality; *P*[Na^+], plasma sodium concentration.

Clinical Significance of Hyponatremia

- Increased risks for osteoporosis, gait instability, falls, and fractures. It is thought that sustained hyponatremia increases oxidative stress and stimulates osteoclastogenesis.
- Increased all-cause mortality in multiple settings (eg, ambulatory setting, emergency department, intensive care unit, geriatric patients, patients with HF or ST-elevation myocardial infarction, cirrhosis, patients receiving kidney replacement therapies)
- Increased postoperative morbidities (eg, major coronary events, wound infections, pneumonia, acute kidney injury [AKI] requiring dialysis, length of hospital stay)
- Predictor of hepatorenal syndrome (HRS) and hepatic encephalopathy in patients with liver disease

Clinical Manifestations of Hyponatremia

- Risk for and severity of neurologic effects depend on the rate of change of $P[Na^+]$. In acute and severe hyponatremia, free water shifts into brain cells to cause brain edema. Severe neurologic complications and death can follow due to the confinement of the brain within the skull.
- Mild: $P[Na^+]$ of 125 mmol/L or more: usually asymptomatic to minimally symptomatic
- Moderate: attention deficit, poor mentation, lethargy, decreased activity of daily living, headaches, nausea/vomiting, disorientation, muscle cramps, reduced reflexes
- Severe: hyponatremic encephalopathy, seizures, coma, respiratory arrest, brainstem herniation, death
- Risks for hyponatremic encephalopathy: children, premenopausal women, postoperative patients, patients with central nervous system (CNS) disorders, lung disease, or hypoxemia

Broad Categorization of Hyponatremia

- Pseudohyponatremia
- Extracellular water shifts due to osmotically active agents in the extracellular space
- True hypoosmolar hyponatremia

Pseudohyponatremia

Mechanism: Pseudohyponatremia refers to falsely low [Na^+] measured from the serum (S[Na^+]). Flame photometric assay is an old method used to detect sodium content via intensity of flame color divided by serum volume. In patients with falsely elevated serum volume due to space-occupying paraproteins or lipids, the S[Na^+], defined as sodium content ÷ serum volume, will be falsely low. Newer techniques of measuring P[Na^+] are now widely used to avoid pseudohyponatremia:

- Ion-specific electrodes measure [Na^+] directly from the plasma.
- Supracentrifugation of serum to remove paraproteins/lipids before measuring S[Na^+]
- P[Na^+] measured from blood gas is not affected by dilution caused by paraproteins or lipids.

Conditions that may present as "pseudohyponatremia"

- Severe hyperlipidemia (eg, hypertriglyceridemia)
- Paraproteinemia (eg, multiple myeloma, Waldenstrom macroglobulinemia)

Management: Pseudohyponatremia requires no treatment.

Extracellular H_2O shift

Mechanism: transient hyponatremia due to extracellular free H_2O shift in the presence of osmotically active agents in the extracellular space

Conditions associated with extracellular H_2O shift

- Hyperglycemia
- Hypertonic mannitol
- Sucrose, maltose (mixed in intravenous [IV] immunoglobulins [IgG, immunoglobulin G] solutions)

Management: Hyponatremia due to transient extracellular H_2O shift will resolve after the treatment of hyperglycemia, eventual excretion of mannitol, or metabolism and/or excretion of sucrose/maltose.

Typical presentation: S_{OSM} of greater than 300 mmol/L due to the presence of osmotic agents

(True) Hypoosmolar hyponatremia

True hypoosmolar hyponatremia refers to truly reduced body Na^+ concentration due to increased free H_2O retention, excessive urinary Na^+ and/or K^+ loss, or both.

Differential Diagnoses of Hypoosmolar Hyponatremia

The differential diagnosis of hypoosmolar hyponatremia is categorized based on volume and ADH status (**Figure 1.3**).

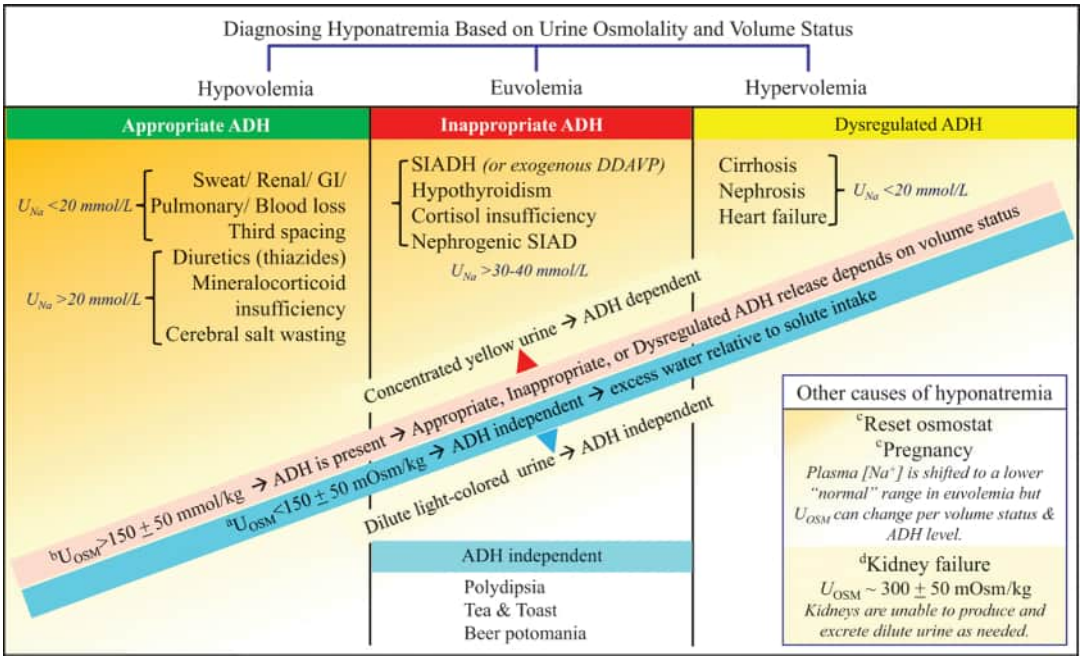


FIGURE 1.3 Differential diagnoses and clinical evaluation of hyponatremia.
Abbreviations: ADH, antidiuretic hormone; GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone secretion; U_{Na}, urine sodium.

[a]Having dilute urine (light yellow shaded area), that is, urine osmolality of less than 150 ± 50 mmol/kg in the setting of hyponatremia suggests that the underlying etiology of hyponatremia is independent of ADH. ADH-independent causes of hyponatremia include polydipsia or excess-free water relative to solute intake, for example, tea and toast or beer potomania.

[b]A concentrated urine (dark yellow shaded area) with osmolality greater than 150 ± 50 mmol/kg suggests the underlying etiology of hyponatremia is driven by ADH, whether it is appropriate, inappropriate, or dysregulated. Assessment of volume status may help identify the underlying etiology.

[c]Pregnant women or individuals with reset osmostat have lower baseline plasma sodium concentrations but they can concentrate or dilute their urine appropriately per volume status and ADH levels.

[d]Individuals with advanced kidney disease are unable to optimally concentrate or dilute their urine per volume status and ADH levels. Their urine osmolality tends to be isosthenuric.

Hypovolemic hyponatremia

Mechanism: appropriate increase in ADH secretion due to volume depletion + free H_2O ingestion in excess of solute intake

Conditions associated with hypovolemic hyponatremia

- Bodily fluid loss, chronic diuretics (thiazides), third spacing
  - Typical presentation: hypovolemia
  - Urine Na^+ concentration ($U[Na^+]$) less than 20 mmol/L, urine osmolality (U_{OSM}) greater than 200 to 300 mOsm/kg
- Renal salt wasting: diuretic use, mineralocorticoid insufficiency (eg, adrenal insufficiency or resistance to mineralocorticoid), cerebral salt wasting (CSW)

Typical presentation: hypovolemia, $*U[Na^+]$ less than 20 to 30 mmol/L, U_{OSM} typically greater than 300 mOsm/kg

NOTE

$*U[Na^+]$ may be greater than 20 to 30 mmol/L in patients with hypovolemia with acute or recent diuretic use, renal or CSW, or advanced kidney failure. Renal reabsorption of sodium may be suboptimal in patients with kidney failure despite hypovolemic status.

Euvolemic hyponatremia: ADH dependent

Mechanism: inappropriate ADH secretion + free H_2O ingestion in excess of solute intake. "Inappropriate" refers to ADH secretion in response to stimuli other than hypovolemia or hyperosmolality.

Conditions associated with "inappropriate" ADH secretion

- *SIADH secretion:* CNS or pulmonary pathology, drugs affecting CNS, antipsychotics, antiepileptics, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclophosphamide, acute pain, nausea/vomiting, hypoglycemia, symptomatic human immunodeficiency virus (HIV), prolonged strenuous exercise
- *Severe peripheral hypothyroidism* (myxedema coma or thyroid-stimulating hormone [TSH] >50 mIU/mL): mechanisms unclear, thought to be due to both ADH-dependent and possibly ADH-independent mechanisms. ADH-dependent mechanism is thought to reflect reduced cardiac output and increased vascular resistance with resultant renal hypoperfusion.

- *Central hypothyroidism* (normal to low normal TSH in the setting of low free thyroxine T4) should be considered in individuals with a history of pregnancy complications (ie, Sheehan syndrome), craniopharyngiomas, cranial irradiation for brain tumors, hematologic malignancies, infiltrative granulomatous disease.
- *Hypocortisolism* leads to increased synthesis of corticotropin-releasing hormone, which may be coexpressed with ADH, hence increased ADH level.
- *Pregnancy*: reduced threshold for ADH secretion and increased thirst sensation

Typical presentation and evaluation for "inappropriate" ADH secretion

- Clinical criteria: euvolemia
- $U[Na^+]$ greater than 20 to 30 mmol/L (on normal dietary water and sodium intake)
- U_{OSM} greater than 100 mOsm/kg and low serum uric acid (assuming relatively good kidney function)*
- Fractional excretion of uric acid of greater than 12% has been suggested to provide a positive predictive value of 100% for the diagnosis of SIADH while a value of less than 8% excludes the diagnosis.
- Rule out hypothyroidism (TSH, free T4) and hypocortisolism (morning cortisol level).

NOTE

*In the setting of hyponatremia induced by excess water relative to solute intake (eg, polydipsia, beer potomania, tea and toast syndrome), ADH secretion is expected to cease to allow healthy kidneys to maximally excrete free water, evidenced by dilute urine (strictly speaking, U_{OSM} should be less than 100 mOsm/kg). On the other hand, any concentrated urine, that is, U_{OSM} greater than 150 ± 50 mOsm/kg, would indicate water is being reabsorbed by renal tubules, suggesting the presence of ADH, whether it be appropriate (due to hypovolemia), inappropriate (unrelated to hypovolemia), or dysregulated (cannot be suppressed due to ongoing low effective circulating volume).

An exception to this rule is seen in older individuals or those with reduced kidney function who are incapable of maximally diluting their urine below 100 mOsm/kg despite having hyponatremia. Having a U_{OSM} of 100 to 200 mOsm/kg in the setting of hyponatremia in these individuals may reflect suboptimal diluting capacity by the kidneys rather than the presence of ADH. Clinical judgment is required.

- Water loading test: In equivocal cases of SIADH, water loading test may be considered. This test may only be performed in patients with mild hyponatremia (NOT in those with moderate or severe hyponatremia). In this test, normal individuals will dilute the urine to U_{OSM} of less than 100 mOsm/kg and appropriately excrete *greater than* 90% of a free water load (given at 20 mL/kg body weight) within 4 hours, whereas patients with SIADH will inappropriately hold on to the free water load. See **Appendix A1.1** for the protocol.

Euvolemic hyponatremia: ADH independent

Mechanisms and laboratory findings depend on specific conditions.
Conditions associated with ADH-independent euvolemic hyponatremia

- *Reset osmostat*
  - Mechanism: Osmotic threshold for ADH release is lowered. The ideal $P[Na^+]$ range in patients with reset osmostat is shifted to a lower level compared with that of the general population. Note that these patients can still respond to volume and osmolality changes, albeit to maintain a lower $P[Na^+]$ "normal range."
  - Conditions associated with reset osmostat: normal variant, hypothalamic injury, malnutrition
  - Laboratory findings: $U[Na^+]$ and U_{OSM} vary according to volume status and S_{OSM}.
- *Primary polydipsia*
  - Mechanism: The ingested water load exceeds the capacity of the kidneys to excrete.
  - Conditions associated with primary polydipsia: patients with psychiatric disorders ± phenothiazines with associated dry mouth, hypothalamic infiltrative disease such as sarcoidosis affecting thirst center, use of mouth-drying medications (eg, anticholinergic agents, decongestants)
  - Laboratory findings: U_{OSM} less than 100 to 200 mOsm/kg; $U[Na^+]$ varies per sodium intake.
- *Tea and toast syndrome, beer potomania*
  - Mechanism: Low solute intake cannot provide adequate solutes required by the kidneys to excrete water.*

FYI

*If the kidneys can excrete water by producing dilute urine of 100 mOsm/kg, the kidneys need 100 mOsm of solute from dietary intake for every one liter of water they excrete. If an individual ingests 800 mOsm solute loads daily and has a diluting capacity of 100 mOsm/kg, this individual can theoretically handle up to 8 L of water ingestion daily without developing hyponatremia. However, if this individual only ingests 200 mOsm of solute load daily, the maximum water excretion volume would be limited to 2 L. If this individual drinks anything more than 2 L of water daily, hyponatremia ensues. This explains why individuals with low dietary intake are prone to developing hyponatremia. Their ability to excrete large volumes of water is limited by their low solute intake.

- Laboratory findings: U_{OSM} less than 100 to 200 mOsm/kg; $U[Na^+]$ varies per intake.

- *Water reabsorption from irrigation fluids* used with genitourinary procedures (eg, transurethral resection, hysteroscopy, nephrolithotomy):
  - 1.5% glycine solution:
    - Solution is hypotonic: osmolality = 200 mOsm/kg.
    - Glycine may also directly stimulate ADH secretion.
  - 3% sorbitol:
    - Solution is hypotonic: osmolality = 165 mOsm/kg.
    - Sorbitol is metabolized to glucose + fructose in liver, then to CO_2 and H_2O.
    - Fructose is also known to stimulate ADH synthesis.
  - Note: 5% mannitol solution usually does not cause hyponatremia because it is isotonic to plasma, with osmolality = 275 mOsm/kg.
  - Laboratory findings: U_{OSM} less than 100 to 200 mOsm/kg; $U[Na^+]$ varies per sodium intake.
- *Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)*
  - Mechanism of disease: X-linked gain-of-function mutation of arginine vasopressin 2 receptor (AVP2R); in this condition, AVP2R are constitutively activated independent of ADH.
  - Typical presentation:
    - Hyponatremia (female carriers may be asymptomatic with mild hyponatremia), decreased thirst, infrequent voiding
    - Laboratory findings are similar to those seen with SIADH, but ADH level is very low or undetectable (in contrast to SIADH where

ADH levels are high).
    - Similar to patients with SIADH, those with NSIAD also have abnormal responses to water loading test.
- Definitive diagnosis requires sequencing of the AVP2R gene.

Hypervolemic hyponatremia

ADH dependent: dysregulated continuing ADH secretion due to conditions associated with reduced effective circulating volume (eg, HF, cirrhosis, nephrotic syndrome [NS])
ADH independent: advanced kidney failure with reduced capacity to excrete free water load

Hyponatremia with variable volume status

Exercise-induced hyponatremia (eg, marathon runner hyponatremia):

- Volume status is variable.
- Mechanisms:
    - Excess-free water ingestion relative to salt and water loss from sweating
    - Concurrent increased ADH level associated with muscle injury during heavy exercise
- Heavy exercisers should be advised to only drink per thirst. Electrolyte-balanced fluid is preferred over electrolyte-free water replacement.

Drug-Associated Hyponatremia

Drugs causing reset osmostat

Antidepressants (venlafaxine), antiepileptics (carbamazepine)

Drugs causing hypopituitarism and adrenal insufficiency

Checkpoint inhibitors (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] inhibitors > anti-program cell death 1 [PD-1, programmed death 1], anti-programmed cell death ligand 1 [PD-1L, programmed death ligand 1])

Drugs affecting both sodium and H_2O homeostasis with net H_2O reabsorption

Diuretics (thiazides, indapamide, K-sparing diuretics > loop diuretics)

Drugs affecting ADH

- **Increased ADH production**: antidepressants (amitriptyline, protriptyline desipramine, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors), antipsychotics (thioridazine, trifluoperazine, haloperidol), antiepileptics (carbamazepine, oxcarbazepine, sodium valproate), chemotherapeutic agents (vincristine, vinblastine, IV cyclophosphamide, melphalan, ifosfamide, methotrexate, interferon α and γ, levamisole, pentostatin, monoclonal antibodies), opioids
- **Potentiate ADH effect**: antiepileptics (carbamazepine, lamotrigine), antidiabetics (chlorpropamide, tolbutamide), anticancer agents (IV cyclophosphamide), NSAIDs

Other important causes of drug-induced hyponatremia

- **DDAVP**: Hyponatremia may easily occur in patients with excessive free water intake while receiving DDAVP for any reason (eg, enuresis, cDI, or von Willebrand disease). Patients must be instructed to only drink water per thirst, adjust DDAVP dose per urine volume, and recognize signs and symptoms of hyponatremia.
- **Angiotensin-converting enzyme inhibitors** (ACEi): ACEi inhibits the conversion of angiotensin I (Ang I) to II (Ang II) in peripheral tissue but not in the brain. In the brain, Ang I is converted to Ang II, which can stimulate thirst and ADH release. Use of ACEi increases Ang I levels, hence increasing brain Ang II. ACEi may also induce increased ADH secretion by delaying bradykinin degradation.
- **IV immune globulins mixed in maltose or sucrose**: Hyponatremia may occur via (1) pseudohyponatremia if measured by flame photometric assay due to a large amount of space-occupying globulins and (2) dilutional hyponatremia due to extracellular free water shift with accumulation of maltose or sucrose.
- **Amphetamines, 3,4-methylenedioxymethylamphetamine (MDMA)** aka "**ecstasy**": increase in hypothalamic ADH secretion and excessive water intake due to associated hyperthermia and thirst. MDMA is a synthetic sympathomimetic amphetamine.

- **Other recreational drugs:** Bath salts (derivatives of cathinone, eg, methylenedioxypyrovalerone, methylone, or mephedrone), cannabis, and synthetic cannabinoids can also be present with hyponatremia.
- **Less common causes**: nicotine patches, colchicine poisoning, dopaminergic agents, unfractionated heparin, hydroxyurea, azithromycin, clonidine, glipizide, tacrolimus, co-trimoxazole, theophylline, proton pump inhibitors

NOTE

Diagnosing the underlying cause of hyponatremia:

- In the setting of hyponatremia, the presence of a dilute urine (ie, U_{OSM} <150 ± 50 mOsm/gk) suggests that the cause of hyponatremia is independent of ADH. Hyponatremic conditions that are independent of ADH include "tea and toast," "beer potomania," polydipsia, and water overload from the use of irrigation fluids.
- A concentrated urine (ie, U_{OSM} >100-150 mOsm/kg) suggests that the hyponatremia is due to increased water reabsorption by renal tubules, indicating the presence of ADH.
  - For hyponatremia with a high U_{OSM}, (ie, >150-200 mOsm/kg), volume assessment would define the nature of ADH (ie, appropriate, inappropriate, or dysregulated) and help narrow down the differential diagnosis.
  - A urine sodium concentration may be used to further confirm a suspected diagnosis.

A summary of the differential diagnosis of hyponatremia categorized based on urine osmolality, volume status, and urine sodium concentration is shown in **Figure 1.3**.

Management of Hyponatremia

General considerations

- Provide adequate **oxygenation** and mechanical ventilation support if necessary. Hypoxemia may exacerbate hyponatremic encephalopathy.
- **Potassium** and sodium are equivalent effective, exchangeable osmoles. Any K^+ given during the treatment of hyponatremia will correct $P[Na^+]$ exactly as if the same amount of Na^+ was given.*

*Example: If a patient needs 200 mmol of Na^+ to achieve the goal $S[Na^+]$ but also needs 75 mmol K^+ for concurrent hypokalemia, the clinician should administer:

125 mmol of Na^+ + 75 mmol of K^+ = 200 mmol total of Na^+ + K^+ *instead of* 200 mmol of Na^+ + 75 mmol K^+

The latter combination would overshoot the goal $S[Na^+]$.

- Monitor **urine output**: Hypotonic polyuria can easily overcorrect hyponatremia if not recognized. Hypotonic polyuria (aquaresis) may be seen during the treatment of hyponatremia with the following conditions: postpituitary infarction, glucocorticoid replacement in patients with cortisol insufficiency, discontinuation of DDAVP in patients with chronic use (eg, for cDI), recovery from acute respiratory failure, withdrawal of thiazides, water deprivation in primary polydipsia, rapid volume expansion with IV boluses of normal saline. Normal saline boluses should be reserved for patients who are hemodynamically unstable.
- Cases of osmotic demyelination syndrome (ODS) have been reported in patients with concurrent **hypokalemia, hypomagnesemia, hypophosphatemia, thiamine** deficiencies, or any combination of these deficiencies *independent* of the rate of Na^+ correction. Monitor and correct these deficiencies during the management of hyponatremia.

Rate of correction

Osmotic demyelination syndrome

- *Rapid correction* can lead to ODS, previously known as central pontine myelinolysis (CPM) due to insufficient time allowed for brain synthesis of organic osmolytes or "idiogenic osmoles" to counteract the acute rise in extracellular osmolality. Major brain organic osmolytes include glutamine, glutamate, taurine, myoinositol, among others.
- *High risks for ODS*: $S[Na^+]$ of less than 105 mmol/L, alcoholism, malnutrition, advanced liver disease, hypokalemia, older age, use of thiazides, ± concurrent hypophosphatemia, hypomagnesemia, thiamine deficiency
- *Clinical manifestations* of ODS:
  - 1 to 2 days: generalized encephalopathy
  - 2 to 3 days: behavioral changes, cranial nerve palsies, progressive weakness, quadriplegia, "locked-in" syndrome; death is possible.
  - Diagnosis: presence of nonenhancing and hyperintense pontine and extrapontine lesions on T2-weighted MRI. A time lag of up to 2 weeks for the presence of MRI abnormalities is possible.

- ODS may be reversible, even in some cases with severe symptoms at presentation.

Correction rate for severe symptomatic (eg, seizures, coma, evidence of increased intracranial pressure) **acute hyponatremia** (known duration <24-48 hours):

- Urgent correction by 5 mmol/L to prevent brain herniation and cerebral ischemia*

NOTE

*An acute 5% increase in P[Na^+] (ie, correction of S[Na^+] by 5 mmol/L) should substantially reduce cerebral edema and decrease intracranial pressure by 50% in individuals who present with severe neurologic complications (eg, seizures, coma).

- *For severe symptoms* (eg, seizures, coma): Infuse 100 mL of 3% NaCl over 10 minutes to break seizures or up to a total of three boluses, whichever comes first.
- *For mild to moderate symptoms with low risk of brain herniation*: Infuse 3% NaCl at 0.5 to 2 mL/kg/h. Must monitor change in *S*[Na^+] closely.
- No need for subsequent restriction in correction rate if acute hyponatremia (ie, hyponatremia duration <48 hours)
- For chronic hyponatremia, the subsequent correction rate should follow limits set for chronic hyponatremia (see the following).

Correction rate for mildly symptomatic or asymptomatic chronic hyponatremia (ie, duration of hyponatremia ≥48 hours)

- *High-risk ODS*: 4 to 6 mmol/L/d; maximum 8 mmol/L/d
- *Normal-to-low risk ODS*: 4 to 8 mmol/L/d; maximum 10 to 12 mmol/L/d but not to exceed 18 mmol/L in any 48-hour period

Reversal of overcorrection

- Reversal has been shown to be beneficial in rats and human case reports.
- Reversal is suggested in individuals with moderate to high risk of ODS and recommended in individuals with high risk of ODS or presenting *S*[Na^+] less than 120 mmol/L.
- Reversal may be done by replenishing hypotonic fluids with or without IV DDAVP 2 to 4 µg. The addition of DDAVP is particularly beneficial

among patients with large-volume aquaresis (ie, dilute urine). Repeat dosing may be necessary in patients whose large-volume aquaresis recurs. In the authors' experience, if large-volume aquaresis recurs, it typically happens 18 to 24 hours following the last DDAVP dose.

Specific treatment options (Table 1.1)

Table 1.1 Treatment options in the management of hyponatremia

Treatment categories	Specific options	Indications and comments
Salt supplement	Sodium chloride tablets	Indication: stable euvolemic SIADH with poor oral intake, end-stage disease (eg, patients with end-stage conditions such as metastatic malignancy with associated SIADH)
	Normal saline	Indication: volume depletion Avoid boluses unless patients are hemodynamically unstable.
	3% Saline	Indication: severe neurologic complications, severe salt wasting (eg, renal or cerebral salt wasting), severe SIADH with urine osmolality ≫300 mOsm/kg in the setting of severe hyponatremia and unclear volume status
	Potassium salt	Indication: presence of concurrent hypokalemia Note that potassium supplement increases $P[Na^+]$ exactly as if the same amount of sodium is given.
Reduce free water intake	Water restriction	[a]Arbitrary recommendation: This is generally ineffective.
Increase free water excretion	Loop diuretics	Indication: volume overload (eg, heart failure, cirrhosis, nephrotic syndrome)
	Vaptans	Indications: SIADH, heart failure (not suggested in patients with cirrhosis or those with severe neurologic complications) Concurrent use with loop diuretic is not recommended.
	Demeclocycline	Indication: SIADH (contraindicated during pregnancy and children due to interference with bone development, nephrotoxicity, photosensitivity)

Treatment categories	Specific options	Indications and comments
	Increase solute intake (eg, protein shakes, urea)	Indication: poor solute intake or malnutrition. Consider nutrition consult.
Miscellaneous	Maintain adequate oxygenation/airway if altered mental status; follow serum magnesium, phosphorus, potassium levels and replete as needed.	

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.

[a]Authors' opinion: For water restriction to be effective, water intake must be significantly less than total daily electrolyte-free water clearance.

Fluid restriction: Consider for euvolemic patients or those with hypervolemia.

- "Fluid" implies all fluid consumed, such as those from drinking and food sources, not just water.
- Restriction volume has been suggested to be 500 mL below the patient's average daily urine volume. Authors' opinion: Restrict daily fluid intake to less than patient's daily electrolyte-free water excretion if possible. See equation below.
- Fluid intake less than urine volume × $(1 - (U[Na^+] + U[K^+])/S[Na^+])$
- Despite its popularity, fluid restriction is often ineffective, particularly in patients with severe SIADH.
- Predictors of likely failure with fluid restriction alone
  - U_{OSM} greater than 500 mOsm/kg
  - $$\frac{U[Na^+] + U[K^+]}{S[Na^+]} > 1$$

A ratio greater than 1 indicates that hyponatremia is due to salt wasting rather than excess-free water intake.

- Baseline urine volume less than 1,500 mL/d
- Increase in $S[Na^+]$ of less than 2 mmol/L/d in 24 to 48 hours on a fluid restriction of 1 L/d or less

Salt supplement

- *Normal saline or salt-balanced solution*: Recommended for patients with hypovolemia. Avoid boluses unless hemodynamically unstable. Rapid

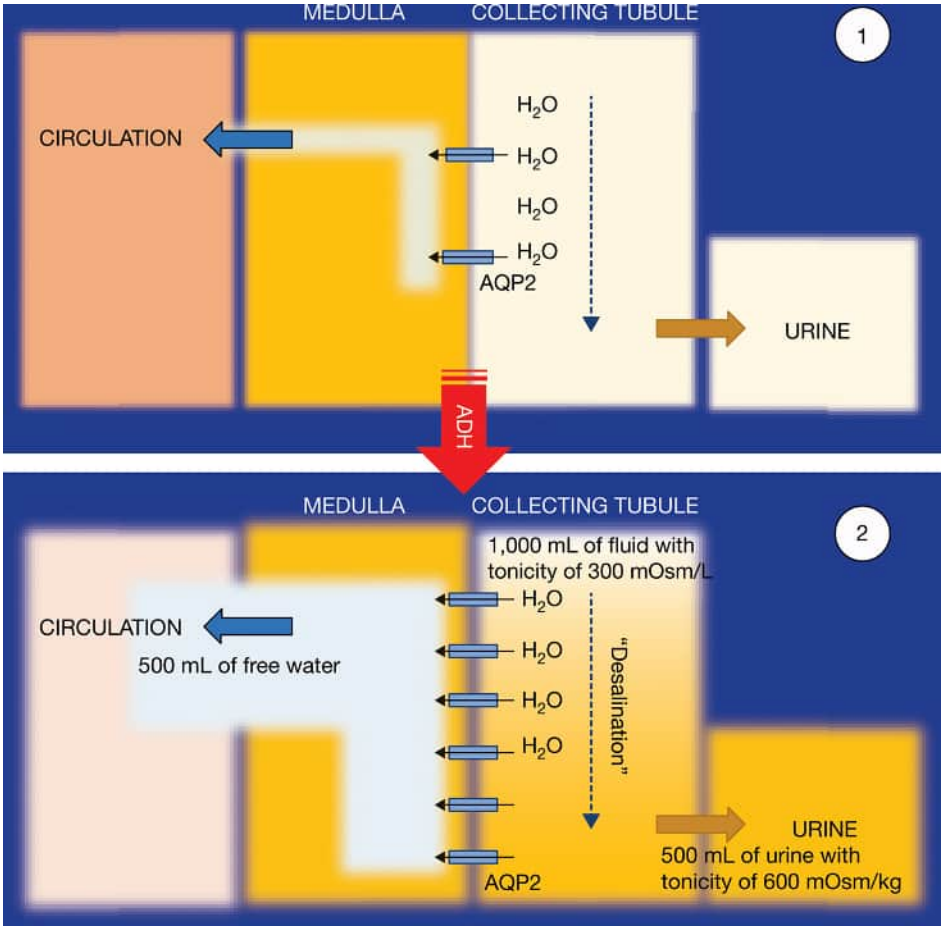
volume expansion can lead to high-volume aquaresis, presumably via acute ADH suppression, hence rapid overcorrection of hyponatremia.

- *Hypertonic saline*:
  - Indicated for patients who are severely symptomatic (eg, seizures, coma)
  - May also be considered at low infusion rates for:
    - Severe SIADH (ie, $U_{OSM} \gg 300$ mOsm/kg) + severe symptomatic hyponatremia

NOTE

Normal saline can worsen hyponatremia in individuals with SIADH with U_{OSM} greater than 300 mOsm/kg. This is due to a process called "desalination" **(Figure 1.4)**.

Bottomline: Any saline solution used in a patient with SIADH for the sole purpose of increasing S[Na^+], the osmolality of this solution must be higher than that of the urine.



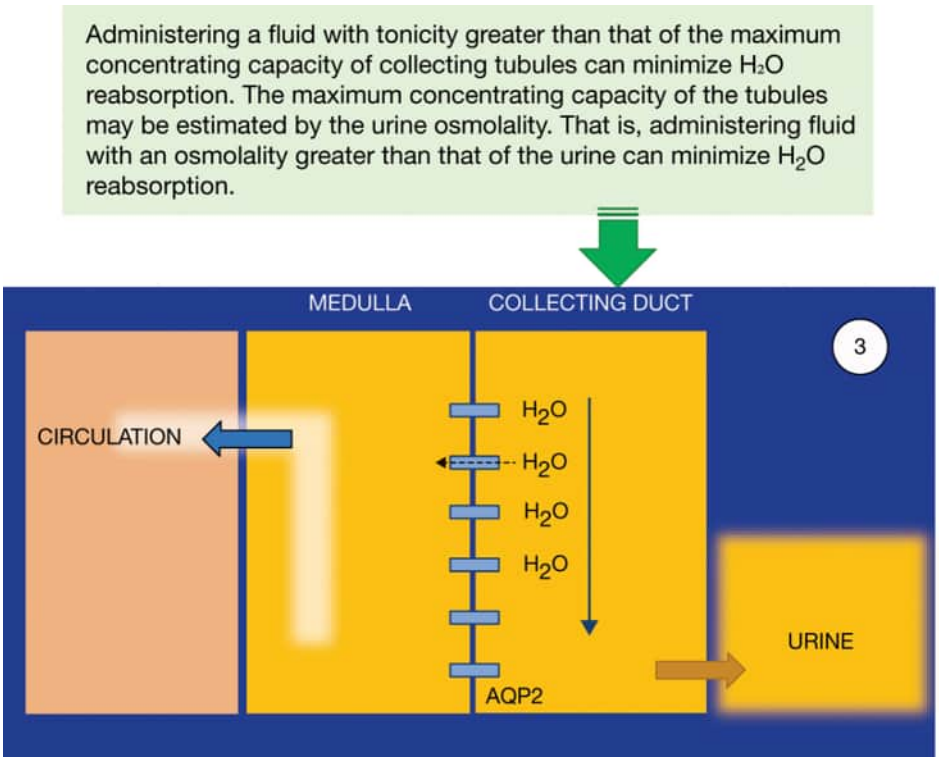

Administering a fluid with tonicity greater than that of the maximum concentrating capacity of collecting tubules can minimize H_2O reabsorption. The maximum concentrating capacity of the tubules may be estimated by the urine osmolality. That is, administering fluid with an osmolality greater than that of the urine can minimize H_2O reabsorption.
MEDULLA
COLLECTING DUCT
3
CIRCULATION
H_2O
H_2O
H_2O
H_2O
URINE
AQP2

FIGURE 1.4 Desalination with the syndrome of inappropriate secretion of antidiuretic hormone. 1. Patient with a low level of antidiuretic hormone: There is a low level of aquaporin 2 (AQP2) expression, thus minimal free water reabsorption. Urine volume is high and urine tonicity is dilute. 2. Patient with syndrome of inappropriate secretion of antidiuretic hormone (SIADH): There is increased AQP2 expression which allows for avid water reabsorption. Imagine a patient with known SIADH who will concentrate any fluid delivered to collecting tubules up to 600 mOsm/kg. If this patient is given 1,000 mL of normal saline with an approximate tonicity of 300 mOsm/L, the kidneys will reabsorb 500 mL of water to produce urine with a tonicity of 600 mOsm/kg. The reabsorbed water leads to a worsening of existing hyponatremia. 3. Administering a fluid with a tonicity greater than that of the maximum concentrating capacity of the tubules can counteract the water-reabsorbing effect of ADH. The maximum concentrating capacity of the tubules may be estimated by the urine osmolality. That is, administering an intravenous fluid (IVF) with an osmolality greater than that of the urine can minimize water reabsorption.

  - Severe salt wasting (eg, severe cerebral or renal salt wasting [cisplatin])
- *Salt tablets*: may be preferred over strict fluid restriction in stable euvolemic patients with SIADH and terminal conditions (ie, metastatic malignancy for a better quality of life—authors' opinion)

Increase renal H_2O excretion

- *Correct underlying disease or any condition* that causes SIADH.

- *Increase dietary solute* load particularly if poor nutrition: parenteral feeding, encourage high oral solute intake (salt and protein)
- *Urea* (0.5-1.0 g/kg/d or higher as needed) may also be used as an osmotic diuretic agent to increase free water excretion in patients with chronic hyponatremia due to SIADH.
- *AVP (ADH) antagonists*:
  - AVP receptor antagonists (aka vaptans, aquaretics): may be used for euvolemic and hypervolemic hyponatremia with dysregulated ADH or SIADH
  - Conivaptan: IV formulation only, combined V1a and V2 receptor antagonist, limit use to 4 days due to significant drug interactions with other agents that are metabolized by CYP3A4.
  - Tolvaptan: oral formulation, V2 receptor antagonist
  - Both agents improve free water excretion and improve *S*[Na^+] without altering 24-hour sodium excretion.
  - Vaptans have not been shown to improve long-term outcomes in the treatment of hyponatremia.
  - Limitations to using AVP antagonists
    - Use of vaptans is not recommended immediately following cessation of other treatments of hyponatremia, particularly 3% saline.
    - Vaptans are ineffective in patients with reduced kidney function (ie, serum creatinine *S*[Cr] >3 mg/dL).
    - Major adverse effects: thirst, hypotension, transaminitis, liver failure (should not be used in any patient for >30 days or in any patient with liver disease), gastrointestinal (GI) bleed
    - Overly rapid correction, particularly if used concurrently with diuretics or in patients without access to free water (eg, patients who are mechanically ventilated or debilitated, bedbound)
    - Data are lacking to recommend vaptans in severe asymptomatic hyponatremia, that is, *S*[Na^+] less than 120 mmol/L.
    - Vaptans should not be used in patients with symptomatic acute hyponatremia, particularly in those with neurologic symptoms due to its delayed onset of action. Hypertonic 3% saline infusion is the treatment of choice in such cases.

- *Demeclocycline*: may be considered in patients with SIADH
  - Mechanism of action is not clear, but thought to reduce aquaporin 2 (AQP2) expression in the renal inner medulla and/or inhibit adenylate cyclase activation by ADH.
  - Adverse effects: rise in blood urea nitrogen (BUN; dose related), dermatitis, transaminitis/hepatitis, hyperphosphatemia, photosensitivity; contraindicated in pregnancy due to discoloration and enamel hypoplasia and retardation in skeletal development in the fetus
- *Loop diuretics*: may be used in patients with hypervolemia. Avoid concurrent use with vaptans due to the risk of overly rapid correction of hyponatremia and hypovolemia.

Special management considerations for patients with NSIAD

- *Conservative therapy*: water restriction, increased salt intake combined with loop diuretic, increase in oral solute intake or oral urea to increase renal H_2O excretion
- *The use of vaptan* is ineffective in all cases with Arg137Cys (arginine to cysteine substitution at amino acid 137) mutation but effective in the F229V (phenylalanine to valine substitution at amino acid 229) mutation. The ineffectiveness of vaptans in specific NSIAD mutations is thought to be due to the inability of vaptans to deactivate the constitutively activated AVP receptor.

Calculations for the correction of hyponatremia

- All calculations are based on the basic concept that plasma sodium concentration is equal to the total amount of sodium (total number of millimoles of Na^+ in the body) divided by total body volume (L). Plasma sodium is measured as serum sodium, denoted here as $S[Na^+]$.

$$S[Na^+] = \frac{\text{Current total body } Na^+ \text{ (mmol)}}{\text{Total body volume (L)}}$$

where
Current total body Na^+ (mmol) = Current $S[Na^+]$ (mmol/L) × total body volume (L)

Total body volume (L) = 0.5 × total body volume (kg) for female or 0.6 × total body volume (kg) for male

- Any change in $S[Na^+]$ depends on the input and output of Na^+ (mmol) as well as the input and output of volume (L):

$$\text{Expected } S\left[Na^+\right] = \frac{\text{Initial total body } Na^+ + Na^+\text{gain} - Na^+\text{loss (mmol)}}{\text{Total body volume} + \text{volume gain} - \text{volume loss (L)}}$$

- Because K^+ is an equivalent effective solute as Na^+ and can affect $S[Na^+]$ similarly as Na^+, K^+ is added to all Na^+ terms.

$$\text{Expected } S\left[Na^+\right] = \frac{\text{Initial total body } Na^+ + \left[Na^+ + K^+\right]\text{gain} - \left[Na^+ + K^+\right]\text{loss (mmol)}}{\text{Total body volume} + \text{volume gain} - \text{volume loss (L)}}$$

- Gains and losses of Na^+ and K^+ and volume can come from the following sources:

Input (gain)	**Oral intake**	**Intravenous fluids (IVF)**
$[Na^+ + K^+]$ gain (mmol)	mmol of $[Na^+ + K^+]$ given by mouth	Total mmol of $[Na^+ + K^+]$ from IVF = $[Na^+ + K^+]$ concentration of IVF (mmol/L) × volume of IVF administered (L)
Volume gain (L)	Volume intake by mouth (L)	Volume of fluid administered (L)
Output (loss)	**Urine**	**GI tract fluids[a]**
$[Na^+ + K^+]$ loss (mmol)	Concentration of $[Na^+ + K^+]$ in urine (mmol/L) × urine volume over period of interest (L)	Concentration of $[Na^+ + K^+]$ in GI fluid (mmol/L) × volume of GI loss over period of interest (L)
Volume loss (L)	Urine volume over period of interest (L)	GI fluid loss over period of interest (L)

[a]GI fluids: vomitus, diarrheal, or biliary fluids.

For *quick calculations involving multiple sources of input and output and estimates for both fluid tonicity and rate administration in clinical practice, use CurbsideConsultant app.*

Correction of hyponatremia in the patient receiving dialysis

- Patients with uremia are thought to be protected from ODS with overly rapid correction of hyponatremia during dialysis because of the simultaneous removal of uremic solutes. However, ODS has been reported in patients with rapid sodium correction with dialysis.
- Correction rates should, therefore, follow the same guidelines for nonuremic patients. See **Appendix A1.2** for:
  - Calculations of blood flow to correct hyponatremia with intermittent hemodialysis (iHD)
  - Calculations for hyponatremia correction using continuous kidney replacement therapy (CKRT)

Management of overly rapid correction of hyponatremia

- For acute water intoxication, relowering of sodium is not necessary.
- For patients with chronic hyponatremia who present with $S[Na^+]$ less than 120 mmol/L, relowering of $S[Na^+]$ should be considered (particularly in patients with high risks for ODS):
- Replace water losses with IV 5% dextrose water or oral water to achieve the desired goal—For patients with hyperglycemia who cannot tolerate high dose of dextrose or oral intake (eg, patient with high serum glucose), 2.5% dextrose water may be used instead.
- Administer DDAVP 2 to 4 µg IV q8h as needed (per Hyponatremia Expert Panel). In our experience, 2 µg DDAVP q12-24h spot dose as needed is typically sufficient. Monitor $S[Na^+]$ closely.
- If overcorrection is due to vaptan, hold the next dose if correction exceeds 8 mmol/L/24 h. In case of unsafe overcorrection, administer free water and DDAVP as above.
- Consider administration of high-dose glucocorticoids to reduce ODS risk in case of severe overcorrection (eg, dexamethasone 4 mg q6h for 24-48 hours).

Management considerations for specific conditions

Hyponatremia in patients with acute decompensated heart failure (ADHF)

- For mild to moderate symptoms:
  - Begin with *fluid restriction* 1 L/d. Add *loop diuretic* as needed for volume overload.

- For severely symptomatic patients with concurrent severe hyponatremia:
  - *AVP receptor antagonist tolvaptan*
  - Although controversial due to safety concerns and lack of long-term benefit, tolvaptan may be considered in patients with ADHF and severe hyponatremia.
  - Avoid concurrent use with loop diuretics due to the potential for overly aggressive diuresis, AKI, and severe electrolyte disturbances.
- Consider the administration of *3% NaCl plus loop diuretics*. Close monitoring is required.

Primary polydipsia

- Behavioral therapy
- Avoid anticholinergic agents, antihistamines, and decongestants due to increased thirst.
- Atypical antipsychotics in patients with psychogenic polydipsia (limited data): clozapine, olanzapine
- If the patient also has hypertension (HTN), consider ACEi, angiotensin receptor blocker (ARB), clonidine, propranolol, or acetazolamide as safely tolerated because these agents have been suggested to benefit primary polydipsia.

FLUID MANAGEMENT

Basic Concepts and Formulas

Osmolar clearance (C_{OSM})

$$C_{OSM} = \frac{U_{OSM} \times V}{P_{OSM}}$$

where U_{OSM} is the urine osmolality, V the is urine volume, and P_{OSM} is the plasma osmolality.

- A typical osmolar clearance is less than 3 L a day.
- C_{OSM} greater than 3 L a day indicates the presence of a solute diuresis.

Urine output (V)

$$V = C_{OSM} + C_{H2O}$$

- Alternatively, $C_{H2O} = V - C_{OSM}$, where C_{H2O} is the free water clearance (FWC).

Free water clearance (Figure 1.5)

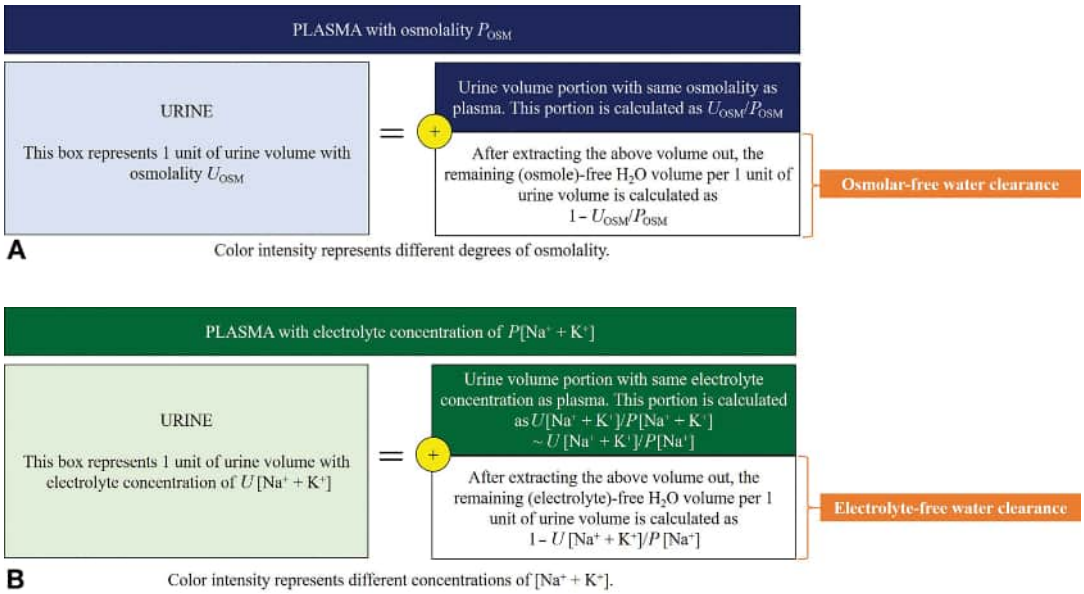

PLASMA with osmolality P_{OSM}
URINE
This box represents 1 unit of urine volume with osmolality U_{OSM}
=
+
Urine volume portion with same osmolality as plasma. This portion is calculated as U_{OSM}/P_{OSM}
After extracting the above volume out, the remaining (osmole)-free H_2O volume per 1 unit of urine volume is calculated as $1 - U_{OSM}/P_{OSM}$
Osmolar-free water clearance
A
Color intensity represents different degrees of osmolality.
PLASMA with electrolyte concentration of $P[Na^+ + K^+]$
URINE
This box represents 1 unit of urine volume with electrolyte concentration of $U[Na^+ + K^+]$
=
+
Urine volume portion with same electrolyte concentration as plasma. This portion is calculated as $U[Na^+ + K^+]/P[Na^+ + K^+] \sim U[Na^+ + K^+]/P[Na^+]$
After extracting the above volume out, the remaining (electrolyte)-free H_2O volume per 1 unit of urine volume is calculated as $1 - U[Na^+ + K^+]/P[Na^+]$
Electrolyte-free water clearance
B
Color intensity represents different concentrations of $[Na^+ + K^+]$.

FIGURE 1.5 Osmolar- and electrolyte-free water clearance. A. The two shades of blue represent two different osmolalities. Dark blue represents plasma osmolality. Light blue represents urine osmolality. The panel on the right represents a "deconstructed" urine as a mixture made up of a portion of fluid with the same osmolality as plasma (calculated as U_{OSM}/P_{OSM}) and a portion of osmolar-free water (calculated as $[1 - (U_{OSM}/P_{OSM})]$). B. The two shades of green represent different concentrations of $[Na^+ + K^+]$. Dark green represents plasma concentrations of $[Na^+ + K^+]$. Light green represents urine concentration of $[Na^+ + K^+]$. The panel on the right represents a "deconstructed" urine as a mixture made up of a portion of fluid with the same $[Na^+ + K^+]$ concentration as plasma (calculated as $U[Na^+ + K^+]/P[Na^+]$) and a portion of electrolyte-free water (calculated as $[1 - U[Na^+ + K^+]/P[Na^+]]$).

- FWC or C_{H2O} = urine volume × $(1 - U_{OSM}/S_{OSM})$
- Conceptually, FWC is the urine volume with an osmolality of zero that remains after the portion of urine normalized to serum osmolality has been extracted/removed from the initial total urine volume.
- Depending on the urine and serum osmolalities, FWC may be positive or negative.

- Positive FWC indicates patients excrete water in excess of that needed to solely clear a solute load (ie, dietary solute load). Examples include polydipsia and diabetes insipidus (DI).
- Negative FWC indicates that the patient's urine is hypertonic than their plasma, thereby gaining free water and lowering plasma osmolality. An example would be that of a patient with SIADH.
- Note that FWC predicts changes in plasma osmolality but *does not* imply a similar directional change in plasma sodium concentration ($P[Na^+]$). For example, a negative FWC increases plasma osmolality, but it does not necessarily imply an increase in $P[Na^+]$. Any change in $P[Na^+]$ depends on the actual amount of salt ($Na^+ + K^+$) gain or loss. This leads to the concept of electrolyte-free water clearance (EFWC).

Electrolyte-free water clearance (see Figure 1.5)

- EFWC = Urine volume × $(1 - U[Na^+ + K^+] \div P[Na^+ + K^+])$
- Since $P[K^+]$ is much lower than $P[Na^+]$, EFWC is typically simplified to:

$$\text{EFWC} = \text{Urine volume} \times (1 - U[Na^+ + K^+] \div P[Na^+])$$

- Essentially, EFWC is the electrolyte-free urine volume that remains after the portion of urine normalized to plasma sodium concentration has been extracted/removed from the initial total volume.
- Depending on the urine and plasma ($Na^+ + K^+$), EFWC may be positive or negative.
- A positive EFWC indicates electrolyte-free water loss which predicts an increase in $P[Na^+]$.
- A negative EFWC implies electrolyte-free water retention and predicts a fall in $P[Na^+]$.

Illustrative Problems

How would the $P[Na^+]$ change in patients with post-acute tubular necrosis (pATN) diuresis below?

- Current $P[Na^+]$: 132 mmol/L, P_{OSM}: 275 mmol/L
- Urine rate of 300 mL/h; U_{OSM}: 450 mOsm/kg, $U[Na^+]$: 70 mmol/L, $U[K^+]$: 15 mmol/L

- EFWC of urine = 0.3 L × (1 − [70 + 15] ÷ 130) = 0.10 L = 100 mL/h of EFWC
- The positive EFWC indicates the patient is losing electrolyte-free water at 100 mL/h.

Answer: Patient's $P[Na^+]$ will be expected to increase with time.

How would the $P[Na^+]$ change (increase or decrease) in the patient below?

- Initial $P[Na^+]$: 130 mmol/L
- Urine output: 4 L, $U[Na^+]$: 35 mmol/L, $U[K^+]$: 15 mmol/L
- Received 5 L of 5% dextrose half normal saline (77 mmol/L of NaCl) over the same period
  - EFWC of urine = 4 L × (1 − [35 + 15] ÷ 130) = 2.5 L
  - EFWC of fluid = 5 L × (1 − 77 ÷ 130) = 2.0 L

Answer: There will be a net loss of 0.5 L of electrolyte-free H_2O, so $P[Na^+]$ would increase.

Can a patient with a urine U_{OSM} greater than P_{OSM} develop hypernatremia?

- Yes, as long as the EFWC is positive.
- Example: patient with U_{OSM} of 500 mOsm/kg, $U[Na^+]$ of 15 mmol/L, $U[K^+]$ of 15 mmol/L, $P[Na^+]$ of 140 mmol/L
  - EFWC = (1 − [15 + 15] ÷ 140) = 0.79
  - Interpretation: For every liter of urine, 0.79 L is electrolyte-free water (free of Na^+ and K^+).

Answer: This *electrolyte-free water loss* would lead to hypernatremia. Although the urine osmolality is high, it is predominantly nonelectrolytes. The high osmolality could come from glucosuria, urea, or any nonelectrolyte solute.

Is free water restriction in the patients with HF below helpful in preventing the worsening of current hyponatremia?

- $P[Na^+]$: 123 mmol/L
- Urine output: 4 L; $U[K^+]$: 15 mmol/L and $U[Na^+]$: 75 mmol/L

- Fluid (water) restriction: 1.5 L

$$\text{EFWC} = 4\ \text{L} \times (1 - [75 + 15] \div 123) = 1.1\ \text{L}$$

Answer: Fluid "restriction" is actually greater than EFWC. The patient actually gains free water over time with this loose fluid restriction. The patient's $P[Na^+]$ will continue to fall.

Can a patient with relatively dilute urine have a solute diuresis (eg, U_{OSM}: 150 mOsm/kg and P[osm]: 277 mmol/L)?

- Yes. Example: same urine and plasma osmolalities above, but patient makes 10 L of urine daily. The total solute load in the urine would be 150 mOsm/kg × 10 L = 1,500 mOsm. An average American diet intake would give a typical urine solute load of approximately 800 mOsm or 10 mOsm/kg/d. 1,500 mOsm is in great excess of 800 mOsm.
- Alternatively, $C_{OSM} = U_{OSM}V \div P_{OSM} = 150 \times 10 \div 277 = 5.4$ L, which is much greater than the typical C_{OSM} less than 3 L/d for an average person on an average diet.

HYPERNATREMIA AND HYPEROSMOLALITY

Background

- Hypernatremia is defined as having $S[Na^+]$ greater than 145 mmol/L.
- Hypernatremia may be due to one or more of the following factors:
  - Inadequate free H_2O intake (eg, limited access to free H_2O or defective thirst sensation)
  - Excessive free H_2O loss
  - Excessive sodium administration
  - Transient intracellular free water shift (usually mild)

NOTE

Hypernatremia typically does not develop unless patients (even in those with DI) have limited access to free water (eg, debility, status post major surgery with the inability to ingest water) or thirst defect.

Clinical Significance

- Serum sodium and mortality follow a U-shaped relationship. Nadir mortality is for patients with $S[Na^+]$ range between 136 and 142 mmol/L.
- Current data involving hospitalized patients reveal a 1.6- to 2.8-fold *higher* odds ratio for mortality in patients with hypernatremia compared to those with hyponatremia.

Clinical Manifestations of Hypernatremia

Lethargy, weakness, irritability, seizures, and intracerebral and subarachnoid hemorrhages due to rupture of cerebral veins with a marked decrease in brain volume, coma, death

Differential Diagnoses of Hypernatremia

Hypernatremia may result from inadequate water intake, excess-free water loss, water loss in excess of salt loss, intracellular water shift, or high salt loading (**Figure 1.6**).

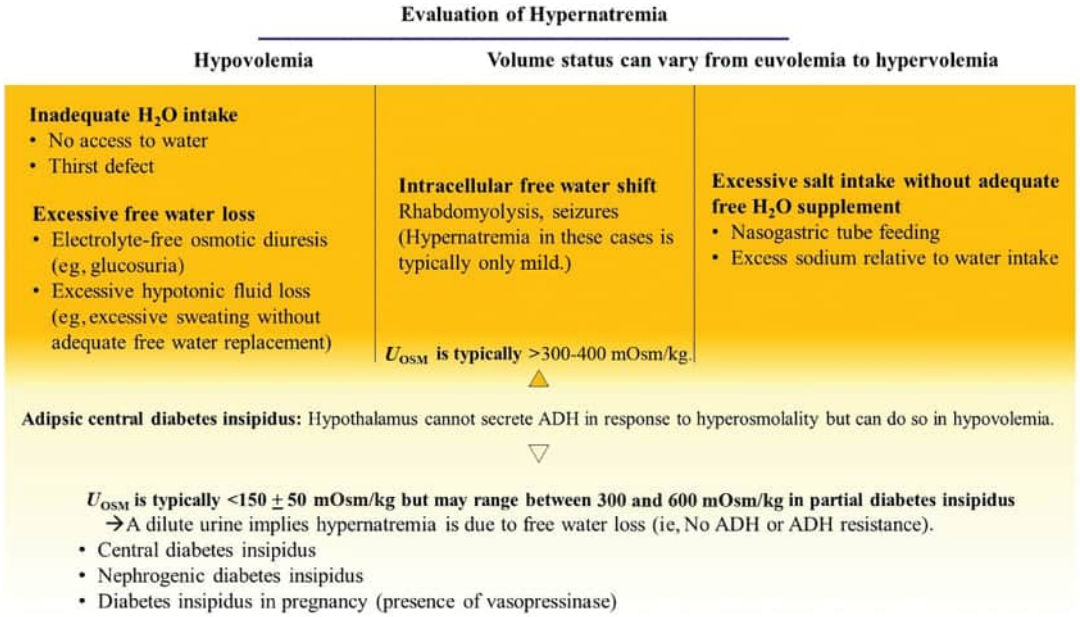

Evaluation of Hypernatremia
Hypovolemia
Volume status can vary from euvolemia to hypervolemia
Inadequate H2O intake
• No access to water
• Thirst defect
Excessive free water loss
• Electrolyte-free osmotic diuresis (eg, glucosuria)
• Excessive hypotonic fluid loss (eg, excessive sweating without adequate free water replacement)
Intracellular free water shift
Rhabdomyolysis, seizures
(Hypernatremia in these cases is typically only mild.)
Excessive salt intake without adequate free H2O supplement
• Nasogastric tube feeding
• Excess sodium relative to water intake
UOSM is typically >300-400 mOsm/kg.
Adipsic central diabetes insipidus: Hypothalamus cannot secrete ADH in response to hyperosmolality but can do so in hypovolemia.
UOSM is typically <150 ± 50 mOsm/kg but may range between 300 and 600 mOsm/kg in partial diabetes insipidus
→A dilute urine implies hypernatremia is due to free water loss (ie, No ADH or ADH resistance).
• Central diabetes insipidus
• Nephrogenic diabetes insipidus
• Diabetes insipidus in pregnancy (presence of vasopressinase)

FIGURE 1.6 Evaluation of hypernatremia based on urine osmolality and volume status.
Abbreviation: ADH, antidiuretic hormone.

Inadequate water intake

Primary hypodipsia—hypothalamic disorder

Poor access to water

Excess-free water loss

High insensible loss: skin (eg, sweating, burn), lungs
Lack of ADH: central, gestational, and adipsic DI

- *cDI* (see "Polyuria" section):
  - Primary/familial cDI: mutation of AVP (ADH) gene
  - Secondary cDI: craniopharyngioma, nonfunctioning adenoma, autoimmune or infiltrative diseases, tumors, prolactinoma, vascular abnormalities, tuberculosis (TB), Rathke cyst, apoplexy
- *Gestational DI*: increased placental production of vasopressinase during pregnancy. Vasopressinase is an enzyme that breaks down ADH and renders it inactive.
- *Adipsic DI* aka "essential hypernatremia" (**Figure 1.7** summarizes the different abnormalities associated with ADH secretion.)

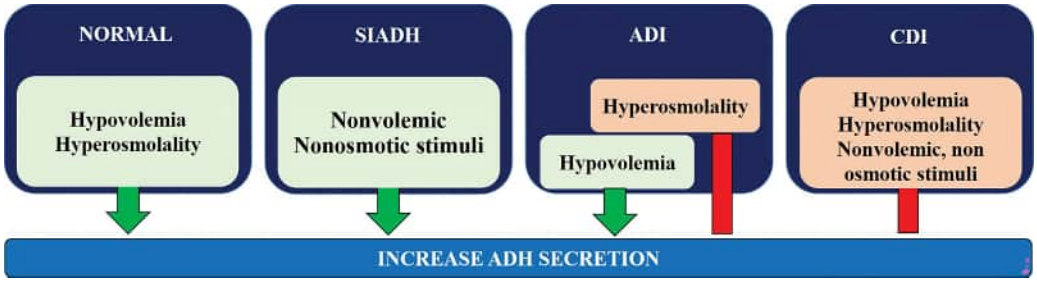


FIGURE 1.7 Conditions with abnormal secretion of antidiuretic hormone. In normal individuals, ADH secretion is stimulated by either hypovolemia or hyperosmolality. In SIADH, ADH secretion is stimulated by conditions other than hypovolemia and hyperosmolality. In ADI, ADH secretion is stimulated by hypovolemia but not hyperosmolality. In addition, thirst defect is also present in ADI. In CDI, ADH secretion cannot be stimulated by anything. Green arrows indicate stimulation. Red bars indicate the absence of stimulation.

Abbreviations: ADI, adipsic diabetes insipidus; ADH, antidiuretic hormone; CDI, central diabetes insipidus; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

- Combined defects in osmoreceptor function AND thirst. Osmolality dependent-ADH secretion is defective, but volume regulated-ADH secretion is intact. Patients with *adipsic* DI cannot secrete ADH in response to a hyperosmolar state but can do so in response to hypovolemia. In contrast, patients with *central* DI cannot stimulate ADH release with either a hyperosmolar or hypovolemic state.

- Clinical manifestations of adipsic DI:
  - Typically asymptomatic due to chronicity of the condition
  - Hypernatremia can be severe, $S[Na^+]$ of approximately 155 to 190 mmol/L.
  - Hypovolemia with associated hyperrenin/hyperaldosterone and hypokalemic metabolic alkalosis may be present.
  - Adipsic DI is associated with obesity, sleep apnea, venous thrombosis during hypernatremic episodes, thermoregulatory dysfunction, seizures, and increased mortality.
  - Causes of adipsic DI: congenital or acquired CNS lesions, for example, post-clipping of the anterior communicating artery (ACA) aneurysms following subarachnoid hemorrhage (osmoreceptors in the hypothalamus derive their vascular supply from small perforating branches of the ACA), post-surgeries for large craniopharyngiomas or suprasellar tumors, neurosarcoidosis, CNS tuberculous infection. Recovery from thirst is uncommon.
- Classic clinical scenario of adipsic DI:
  - Hypernatremia does not correct with free water administration during the euvolemic state. Osmolality dependent-ADH secretion is defective. The lack of ADH impairs optimal free water reabsorption. *HOWEVER,*
  - Hypernatremia can be corrected with free water administration during the hypovolemic state. Volume regulated-ADH secretion is intact. The presence of ADH promotes optimal free water reabsorption.
  - Unlike patients with central DI, the patient with adipsic DI is able to concentrate urine overnight (ie, increased U_{OSM} in the morning) due to increased ADH secretion with relative volume depletion from being nil per os (NPO) while sleeping.
- Treatment of adipsic DI is DDAVP.

Resistance to ADH: nDI

- *Hereditary nDI*: mutation of AQP2 or AVP V2R (vasopressin receptors)
  - AVP V2R mutations are X-linked and account for 90% of congenital nDI.

    - AQP2 mutations are typically autosomal recessive and less commonly autosomal dominant.
- *Secondary nDI*: hypercalcemia, hypokalemia, pregnancy, lithium, demeclocycline, methoxyflurane, foscarnet, aminoglycosides, amphotericin B, cidofovir, vaptans
- *Lithium-induced nDI*:
    - Li-induced nDI is thought to be via its luminal entry into the epithelial sodium channel (ENaC).

> **FYI**
>
> Mechanisms of lithium-induced nDI include downregulation of AQP2 and interference with the formation of a strong medullary concentration gradient. Lithium has been shown to inhibit adenylate cyclase, thereby reducing cyclic adenosine monophosphate (cAMP) formation in the collecting duct and downregulating the expression of AQP2 and the urea transporter UT-A1. The latter reduces urea accumulation in the inner medulla, hence the medullary concentration gradient required for water reabsorption.

- *Sevolfurane-induced nDI*: Sevolfurane, a halogenated inhalational anesthetic used for the induction and maintenance of general anesthesia, has been reported to be associated with nDI in the intensive care setting.

Water loss greater than sodium loss (ie, loss of bodily fluids with lower salt content than that of plasma)

Extrarenal loss: skin (burns, excessive sweating), GI tract (nasogastric suction, viral gastroenteritis, nonelectrolyte osmotic diarrhea, eg, lactulose, vomiting)
Renal loss: loop diuretics, osmotic diuresis (hyperglycemia, mannitol, high-protein diet, tissue catabolism, urea), postobstructive diuresis, post-ATN diuresis

Intracellular water shift

- Transient intracellular water shift typically only causes mild hypernatremia.
- May occur with seizures or rigorous exercise, rhabdomyolysis. The associated increase in intracellular metabolism leads to the breakdown

of larger molecules into many smaller molecules, causing an increase in intracellular osmolality and subsequent intracellular free H_2O shift.

High sodium load

Hypertonic sodium chloride or bicarbonate: administration of hypertonic saline or $NaHCO_3$ (eg, excessive $NaHCO_3$ administration during code or inadvertent mixing of two to three ampules of $NaHCO_3$ in normal saline instead of 5% dextrose water). Note that one (50 mL) ampule of 7.5% $NaHCO_3$ contains 45 mmol/L of Na^+; one ampule of 8.4% $NaHCO_3$ contains 50 mmol/L of Na^+.

Permissive hypernatremia: This is recommended by the Brain Trauma Foundation Guidelines for severe traumatic brain injury. The goal is to achieve $S[Na^+]$ between 150 and 155 mmol/L with the use of 3% saline. Improvement in outcome is unclear.

Salt poisoning: Acute salt poisoning (eg, accidental salt feeding babies [using salt instead of sugar or baby formula] – 1 teaspoon of sodium chloride contains 104 mmol Na^+); intrauterine instillation of hypertonic saline for abortion; saltwater ingestion

Primary mineralocorticoid excess: Hypernatremia may be due to:

- Increased sodium uptake via ENaC
- Chronic sodium retention/volume expansion causing mild chronic ADH suppression
- Presenting $S[Na^+]$ is mildly elevated, approximately 143 to 147 mmol/L
- The use of diuretics (eg, mineralocorticoid receptor antagonists [MRAs] or epithelial sodium channel inhibitors [ENaCi]) corrects the volume expansion and releases the chronic suppression of ADH. Once ADH is synthesized and released, free water reabsorption ensues to correct the hypernatremia.

Diagnosis of Hypernatremia

In addition to obtaining a full medical history, the diagnosis of hypernatremia relies primarily on the assessment of urine osmolality and volume status (see **Figure 1.6**).

- U_{OSM} greater than 300 mOsm/kg generally suggests inadequate water intake, osmotic diuresis, excessive extrarenal fluid loss, intracellular water shift, or accidental salt overdose.

- U_{OSM} between 300 to 600 mOsm/kg may suggest poor renal concentrating ability for conditions listed above or partial diabetes insipidus.
- U_{OSM} less than 300 mOsm/kg indicates excessive renal water loss, eg, central, nephrogenic, or gestational diabetes insipidus.
- Increasing U_{OSM} with hypovolemia but not euvolemia may suggest adipsic diabetes insipidus.

Management of Hypernatremia

Estimating water deficit, assuming optimal $S[Na^+]$ is 140 mmol/L:

$$\text{Water deficit} = \text{Total body volume} \times (S[Na^+] \div 140 - 1)$$

where total body volume may be estimated as:

$$0.5 \times \text{body weight (kg) for females and}$$

$$0.6 \times \text{body weight (kg) for males}$$

Correction rates

- Acute onset (minutes to hours), for example, acute salt poisoning: rapid infusion of 5% dextrose water (or 2.5% dextrose water if hyperglycemia is a problem) to rapidly lower sodium level; may consider emergent hemodialysis in case of acute and severe hypernatremia
- 1 to 2 days onset: Correct $S[Na^+]$ by 2 mmol/L/h until normalization.
- 2 or more days or unknown duration: Decrease $S[Na^+]$ by 8 to 10 mmol/L/d, maximal rate of 0.5 mmol/L/h
- Note, however, that there is now more evidence to suggest that correction rates per current guidelines may be too conservative and may lead to undertreatment of hypernatremia.

Fluid selection

- Fluid selection depends on hemodynamic stability and degree of salt loss.

- For patients experiencing hemodynamic instability and hypotension, use normal saline or lactated ringer (LR) for rapid intravascular expansion.

NOTE

- LR contains potassium and calcium and should not be used in large volumes in patients with hyperkalemia or hypercalcemia.
- Lactate is hepatically metabolized to bicarbonate and should not be used in patients with severe hepatic insufficiency (eg, shock liver).
- Lactate is a substrate for both hepatic and renal gluconeogenesis which may increase glucose concentration in patients with diabetes mellitus (DM).

- For hemodynamically stable patients with:
  - Recent or ongoing salt loss: Use 2.5% or 5% dextrose in ¼ normal saline or ½ normal saline.
  - Pure water loss or salt poisoning: Use 2.5% or 5% dextrose water.
  - Volume overload (eg, decompensated HF and hypernatremia): Use loop diuretic PLUS 2.5% or 5% dextrose water. Do not use furosemide alone because furosemide produces hypotonic urine and can worsen hypernatremia.

Etiology-specific treatment considerations

- For any reversible cause, treat the underlying disease or condition.
- **Central diabetes insipidus**: DDAVP (oral, nasal spray, subcutaneous, or IV). In the case of nasal mucosal inflammation or mechanical ventilation, avoid nasal spray.
- **Nephrogenic diabetes insipidus**
  - Thiazides
    - Thiazide induces volume depletion, thus enhancing proximal sodium and water reabsorption, thereby reducing filtrate flow to the distal nephron for excretion.
    - Thiazide also inhibits carbonic anhydrase in proximal tubules, resulting in increased filtrate/chloride delivery to the macula densa, followed by decreased glomerular filtration via tubuloglomerular feedback (TGF).
  - Prostaglandin (PG) inhibitors (indomethacin, 2 mg/kg/d). PG inhibitors are thought to reduce free water excretion by (1)

increasing AQP2 expression via release of prostaglandin E2 (PGE2) inhibition on adenylyl cyclase activity, hence downstream cAMP stimulatory effect of AQP2 expression, (2) increasing medullary solute reabsorption and maintaining medullary hypertonicity for optimal free water reabsorption.

- **Lithium-induced nDI** (via downregulation of AQP2 expression):
  - Amiloride may be used to reduce renal uptake of Li via principal cells in the collecting duct. This agent may be used in patients who require continuing use of lithium.
  - Acetazolamide has also been shown to reduce polyuria in Li-induced nDI. Mechanism is likely due to a reduction in glomerular filtration rate (GFR) through the enhancement of TGF response.
  - Thiazide diuretics may also be considered as mentioned earlier.
  - Statins have been shown to increase the expression of AQP2 in renal tubules in mice. Further human studies are ongoing.
  - Avoid excess dietary solute load because this can increase free water excretion. (Nutrition consultation is recommended to avoid malnutrition.) In contrast to patients with polyuria due to reduced medullary concentration because of malnutrition, increased protein intake is necessary to rebuild the medullary concentration gradient.
- **Kidney failure, anuric**
  - Free water replacement if hypovolemic
  - Dialysis if volume overload: Calculation is similar to hyponatremia (**Appendix A1.2**).
- **Adipsic diabetes insipidus**: DDAVP
- **Primary mineralocorticoid excess**: low dose diuretic (mineralocorticoid antagonist)

SALT EXCESS

Regulation of Fluid Exchange Between Plasma and Interstitium

FYI

Starling Law

Net filtration = LpS × (Δhydraulic pressure − Δoncotic pressure)

$= LpS \times ([P_{CAP} - P_{IF}] - s[\pi_{CAP} - \pi_{IF}])$

where Lp is the permeability or porosity of the capillary wall, S is the surface area available for filtration, P_{CAP} is the capillary hydraulic pressure, P_{IF} is the hydraulic pressure from interstitial fluid, π_{CAP} is the capillary oncotic pressure, π_{IF} is the interstitial fluid oncotic pressure, and s is the reflection coefficient of proteins across the capillary wall (with values ranging from 0 if completely permeable to and 1 if completely impermeable).

- Normally, there is a small mean gradient of approximately 0.3 mm Hg favoring fluid filtration/extravasation out of the vascular into interstitial space. The extravasated fluid provides nutrients and oxygen to surrounding tissues then returns to central circulation via lymphatics.
- Edema formation occurs when there is any alteration in one or more of Starling forces.
  - ↑Capillary hydraulic pressure
  - ↑Capillary permeability
  - ↑Interstitial oncotic pressure
  - ↓Plasma oncotic pressure

OR

- Lymphatic obstruction
- Avid renal sodium and water retention
- Common edematous conditions including HF, cirrhosis, nephrosis, and kidney failure.

Heart Failure

Mechanism of edema formation in HF

- With reduced cardiac function, cardiac output, and effective circulating volume, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and ADH are stimulated to increase Na^+ and free H_2O retention to increase plasma volume.
- In early HF, the increased plasma volume enhances cardiac contractility, hence cardiac output (Frank-Starling curve).
- As the underlying cardiac disease progresses, the continuing accumulation of plasma volume reaches a point where cardiac contractility reaches its maximum. Further Na^+ and H_2O retention leads

to a severe volume-overloaded state that stifles cardiac contraction, leading to reduced cardiac output and acute decompensated HF (ADHF).

2022 American Heart Association/American College of Cardiology/Heart Failure Society of American (AHA/ACC/HFSA) heart failure guideline, Heidenreich PA et al:

Heart failure: is defined as having symptoms and/or signs of HF caused by structural/functional cardiac abnormalities and at least one of (1) elevated natriuretic peptides or (2) objective evidence of cardiogenic pulmonary or systemic congestion

Spectrum of HF includes:

- HF with preserved ejection fraction (HFpEF) of greater than 50%
- HF with reduced ejection fraction (HFrEF) of 40% or less
- HF with improved ejection fraction (HFimpEF) with previous ejection fraction (EF) of 40% or less and follow-up EF of greater than 40%
- HF with mildly reduced ejection fraction (HFmrEF) of 41%-49%

HFpEF

Diagnosis: H_2FPEF score of greater than 6 points is highly diagnostic of HFpEF; **H**eavy body mass index of 30 kg/m^2 or more (2 points), on 2 or more anti**H**ypertensives (1 point), atrial **F**ibrillation (3 points), pulmonary HTN (**P**ulmonary arterial systolic pressure >35 mm Hg on Doppler echocardiography) (1 point), **E**lder (age >60 years) (1 point), **F**illing pressure (*E*/*e*′ >9 on Doppler echocardiography) (1 point)

HFpEF in women

- Women tend to have higher EFs and more preserved left ventricular global longitudinal strain compared with men, which may make them less likely to develop HFrEF.
- A history of preeclampsia is associated with an increased risk for subsequent HFpEF.

HFpEF mimics: "Clinical diagnosis of HF and EF of 50% or more with a primary noncardiac cause (kidney or liver disease) or an underlying cardiac cause (infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF)"

Comorbidities associated with HFpEF: HTN, diabetes, atrial fibrillation, obesity, coronary artery disease, renal dysfunction

Management of selected comorbidities that contribute to the presentation of HFpEF:

- *Hypertension*: target systolic blood pressure (SBP) of less than 130 mm Hg if safely tolerated
  - The choice of antihypertensive agents depends on tolerability, cost, comorbidities, and societal recommendations.
  - Unless there is a specific indication (eg, rate control for atrial fibrillation), β-blockers are generally avoided given the negative chronotropic effects that may reduce tolerability in HFpEF.
- *Diabetes mellitus*
  - Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are first-line therapy for DM type 2.
  - Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are an option in those with high cardiovascular risk and/or obesity. GLP1-RA has been shown to benefit atherosclerotic cardiovascular outcomes and HF hospitalizations.
  - Metformin is a safe, affordable additional agent for patients with an estimated glomerular filtration rate (eGFR) of equal to or greater than 30 mL/min/1.73 m^2.
  - Finerenone in diabetic kidney disease with eGFR greater than 25 mL/min/1.73 m^2

FYI

Finerenone is a bulky nonsteroidal MRA. Compared with spironolactone and eplerenone, finerenone is the most short acting (half-life 2-3 hours compared with >20 hours and 4-6 hours for spironolactone and eplerenone, respectively) and has the highest selectivity for the mineralocorticoid receptor and least antihypertensive effect. Finerenone has no antiandrogenic effect. The use of finerenone is U.S. Food and Drug Administration (FDA) approved for risk reduction in GFR decline, cardiovascular death, nonfatal heart attacks, and HF hospitalization in adults with chronic kidney disease (CKD) associated with DM type 2. Finerenone has also been shown to reduce proteinuria. The hyperkalemic effect of finerenone has been shown to be slightly less than that of spironolactone.

- *Chronic kidney disease*

- CKD is a risk factor for incident HFpEF with a prevalence of approximately 50% in individuals with HF.
- HFpEF with concurrent CKD is associated with an increased risk of hospitalization and up to a 3-fold increase in mortality.
- Agents that reduce CKD progression in individuals with diabetic kidney disease include ACEi, ARBs, SGLT2i, and the nonsteroidal, selective MRA finerenone. Potassium must be monitored closely with the use of ACEi, ARB, and finerenone.
- A small decrement in eGFR is expected with the use of SGLT2i and MRA and such a change should not be ascribed to AKI.

- *Use of diuretics in HFpEF with concurrent CKD*
  - Evidence-based diuretic agents such as MRA and SGLT2i are preferred.
  - Loop diuretic should be used at the lowest effective dose.
  - Thiazide diuretics may be useful in combination with loop diuretics for more effective diuresis. Monitor electrolytes (eg, sodium and potassium) closely.

Guideline-directed medical therapy (GDMT) for HF

GDMT should be considered for all patients with current or prior HF. GDMT includes four classes of medications.

Sodium-glucose cotransporter-2 inhibitors

- SGLT2i is recommended in symptomatic patients with chronic HFrEF to reduce hospitalization and cardiovascular mortality, regardless of the presence of DM type 2 (Class of recommendation [CoR] 1a).
- SGLT2i can be beneficial in patients with HFmrEF and HFpEF.
- Of interest, the use of empagliflozin was associated with reduced discontinuation of MRAs, possibly due to reduced risk for hyperkalemia.

Renin-angiotensin system inhibitors (RASi)

- *ARB-neprilysin inhibitor (ARNi)* combination, for example, sacubitril/valsartan Entresto*
  - Reduces risk of cardiovascular death and hospitalizations for HF in adult patients with chronic HF
  - Benefits are most evident in patients with EF below normal.
  - Contraindicated in individuals with a history of angioedema

FYI

*Neprilysin is an enzyme that cleaves and inactivates vasodilators including natriuretic peptide, substance P, and bradykinin. A neprilysin inhibitor inhibits the breakdown of vasodilators and reduces blood pressure (BP), hence myocardial workload. However, neprilysin also breaks down angiotensin II (Ang II). The use of a neprilysin inhibitor can thus increase the Ang II level and negate its beneficial vasodilating effects. For this reason, neprilysin inhibitors must be used together with an agent that reduces Ang II levels, which could theoretically be either ACEi or ARBs. However, since both neprilysin inhibitors and ACEi increase bradykinin levels hence angioedema risks, the use of an **AR**B with **n**eprilysin **i**nhibitors was selected over ACEi, hence "**ARNi**." Concurrent use of ARNi with ACEi is contraindicated. A minimum of 36 hour-washout period is required for patients switching from an ACEi to ARNi.

- *ARB alone*: ARB may be used when ARNi is indicated but contraindicated due to adverse effects or costs.
- *ACEi*: ACEi should be used to prevent symptomatic HF and reduce mortality in patients with EF 40% or less who cannot take ARNi or ARB.

Mineralocorticoid receptor antagonists

- Benefits of MRA after myocardial infarction have mostly been shown in patients with symptomatic HFrEF.
- Significantly improves measures of diastolic function in individuals with HFpEF
- Provides balanced diuresis, HTN control, and reduced HF hospitalizations in individuals with HFpEF

β-blockers should be used in patients with HFrEF with EF 40% or less to prevent symptomatic HF.

NOTE

Notes about GDMT in HF

- HFpEF (EF >50%): All individuals with HFpEF should be treated with an SGLT2i unless there is a contraindication. For those with an EF less than 55% to 60%, the use of an MRA, ARNi, or ARB may be considered.
- HFrEF (EF ≤40%): SGLT2i, ARNi, MRA, β-blockers, and diuretics may be started simultaneously at initial (low) doses recommended for HFrEF or sequentially per clinical or other factors.
- It is recommended that GDMT be continued in patients with HFimpEF, including those who are asymptomatic, to prevent relapse of HF and left ventricular dysfunction.
- For African Americans with New York Heart Association Class (NYHA) III-IV who remain symptomatic despite GDMT, the addition of hydralazine and isosorbide dinitrate is recommended (CoR 1).

Use of diuretics in ADHF

- Loop diuretic is often initiated IV at a dose that is twice the patient's usual home diuretic dose, administered multiple times daily.
- Continuous furosemide infusion is equivalent to bolus therapy in terms of efficacy.
- Continuous infusion has a lower risk of ototoxicity than bolus therapy.
- Outpatient bumetanide or torsemide has better bioavailability than furosemide.
- For diuretic resistance: Combine loop with an MRA or thiazide.
- Diuretics should not be discontinued prematurely because of small changes in SCr. Elevations in the range of 0.3 mg/dL do not predict worse outcomes except when patients are discharged with persistent congestion. In addition, SCr may already be on the rise due to ATN that occurred immediately before hospitalization. The continuing rise in SCr is not necessarily the result of ongoing diuretic use. Clinical judgment for continuing diuresis based on patient's level of congestion is required.
- After discharge, the use of ACEi/ARB, MRA, and β-blockers may decrease recurrent congestion requiring hospitalization in HFrEF.

Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy. See **Appendix A1.3**.

Aquaretics

- Vaptans: AVP V2R antagonists
- The use of vaptan for HF is not included in the 2022 AHA/ACC/HFSA Heart Failure Guideline. This is likely due to lack of benefit data.

FYI

The use of vaptans in ADHF

- Early benefit in dyspnea and edema/weight, but no benefit on HF, hospitalization, or mortality in earlier study (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan [EVEREST] trial).
- 2017 TACTICS-HF trial (Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure), n = 257: In patients hospitalized with ADHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders at 24 hours, despite greater weight loss and fluid loss. Responders were

defined as having at least moderate improvement in dyspnea, without death or the need for rescue therapy.

Drugs to *avoid* in patients with HF

Dipeptidyl peptidase-4 (DPP4) inhibitors

- Saxagliptin: increased risk of HF hospitalization
- Alogliptin: increased signal for HF

Thiazolidinediones (TZD): risk of fluid retention, weight gain, and HF events in individuals with or without a previous history of HF, possibly due to increased renal sodium reabsorption. This risk is increased when used in combination with insulin therapy.

TZD and nondihydropyridine calcium channel blockers (CCBs): In patients with EF 50% or less, TZD and nondihydropyridine CCBs with negative inotropic effects (eg, diltiazem, verapamil) may be harmful.

Patients with suspected amyloid should undergo screening for monoclonal light chains. If negative, confirm the presence of transthyretin amyloid with bone scintigraphy. Genetic testing is recommended to differentiate hereditary variant from wild type.

- Tafamidis is recommended in select patients with wild type or variant transthyretin amyloid to reduce cardiovascular morbidity and mortality.
- Anticoagulation is reasonable in patients with cardiac amyloid and atrial fibrillation to reduce risk of stroke.

Vasodilators, inotropes, vasopressors

- Overall, there are no data suggesting that IV vasodilators (eg, nitroglycerin or nitroprusside) improve outcomes in patients hospitalized with HF. Thus, the use of IV vasodilators is limited to the relief of dyspnea in patients without hypotension who are hospitalized for HF.
- Patients with known systolic HF (low EF) and with signs of shock or hypotension: IV inotropes (eg, dobutamine or milrinone)
- Patients with diastolic HF with signs of shock or hypotension: IV vasopressor (phenylephrine) may be used—Do not give inotrope.
- Unknown cardiac status with signs of shock or hypotension: IV inotropes (eg, dobutamine or milrinone), ± vasopressor and mechanical support

Nephrotic Syndrome

Clinical manifestations

Proteinuria of 3.5 g/d or more, hypoalbuminemia (as measured by bromocresol purple, capillary electrophoresis, or immunonephelometric methods, not by bromocresol green—the latter can give erroneously high albumin levels), hyperlipidemia, edema

Mechanisms of edema formation in NS

Underfilling theory

- Hypoalbuminemia due to urinary loss and inadequate hepatic compensatory albumin synthesis reduces intracapillary oncotic pressure, thus "underfilling" the arterial bed. This leads to stimulation of the RAAS, SNS, and ADH systems to promote renal sodium and water retention.
- This theory has been challenged by many observations:
  - NS-associated edema may improve with improvement of the underlying kidney disease *before* any rise in serum albumin.
  - Individuals with congenital analbuminemia *do not* develop edema.

Overfilling theory

Edema is due to avid renal sodium retention induced by the underlying diseased kidneys. This occurs via:

- Increased Na^+-K^+-ATPase and ENaC activities in cortical collecting tubules. Proteins filtered into tubular lumen may contain proteases (plasmin) that can cleave and activate ENaC, thereby enhancing sodium reabsorption.
- Relative renal resistance to atrial natriuretic peptide and urodilatin
- Increased AQP2 expression in renal tissues

Other possible contributor to edema formation: increased vascular permeability

Management of NS (KDIGO 2021, Kidney International 2021)

Edema

- Mainstay of therapy is the use of loop diuretics.
  - Acute diuretic resistance "braking phenomenon" may occur with repetitive use of furosemide.

    - Some evidence suggests a more favorable pharmacokinetic profile with longer-acting bumetanide and torsemide compared with furosemide (from HF studies).
    - Continuous infusion with loop diuretic lowers ototoxicity compared with boluses.
- Loop diuretics can be used with or without one of the following for additive effect:
    - Thiazides: Administer 2 to 5 hours before loop diuretic for peak drug level and maximize blockade of distal sodium reabsorption.
    - ENaCi (eg, amiloride)—based on mechanism of edema; randomized controlled trials to assess efficacy are lacking.
    - Addition of salt-poor albumin has not been shown to increase sodium excretion in patients with NS or cirrhosis with mean serum albumin of 3 g/dL or greater. Benefits of albumin infusion for patients with NS and albumin less than 3 g/dL are not known.

Proteinuria

- Proteinuria measurements: 24-hour urine collection is preferred, followed by protein-to-creatinine ratio (uPCR) from a shorter timed collection (eg, 12 hours), and lastly, spot uPCR at the same time of day and under similar conditions of physical activity in otherwise stable patient. Of note, first morning proteinuria collection may underestimate 24-hour proteinuria in cases of orthostatic proteinuria.
- Renin-angiotensin-aldosterone system inhibitors (RAASi): Use maximal dose of ACEi or ARB as safely tolerated to treat patients with proteinuria. Dual therapy may be synergistically beneficial at the cost of greater adverse effect profile (eg, hyperkalemia, AKI) and is generally avoided. Instruct patients to self-reduce dose during volume depleted state.
- Dietary sodium restriction (eg, <2 g/d) in patients who fail to achieve proteinuria reduction. Strict sodium restriction may reduce proteinuria/albuminuria independent of BP control. Mechanisms are unclear.
- Consider addition of an MRA (eg, spironolactone, eplerenone, finerenone) but with caution to monitor serum potassium levels. Finerenone is a third-generation potent, nonsteroidal selective MRA. Compared with currently available steroidal-based MRAs, finerenone

has greater selectivity for the mineralocorticoid receptor but very low affinity for androgen, glucocorticoid, and progesterone receptors. Currently available data have shown that finerenone confers greater anti-inflammatory and antifibrotic efficacy compared with spironolactone and eplerenone.

Hypertension

- Current data support a *goal systolic blood pressure of 120 mm Hg* in patients with glomerular disease.
- *First-line agents*: ACEi or ARB
- *Second-line agents*: MRA (or direct renin inhibitor [DRI]—although DRI is not commonly used)
- *Loop and thiazide diuretics* improve BP control while offsetting the hyperkalemic effect of RAASi and enhancing the antiproteinuric effects of RAASi.
- *Antihypertensive agents with antiproteinuric effect*: Nondihydropyridine CCBs (eg, diltiazem, verapamil) are preferred over β-blockers, diuretics, α-1 blockers. Dihydropyridine CCB, methyldopa, and guanfacine do not improve and may even worsen proteinuria.

Hyperlipidemia

- Treatment of hyperlipidemia may be considered in NS, particularly in the presence of other cardiovascular risk factors including HTN and DM.
- Lifestyle modification: heart-healthy diet, increased physical activity, weight reduction, smoking cessation
- Consider starting a *statin as first-line therapy*:
  - Assess atherosclerotic vascular disease (ASCVD) risk based on low-density lipid LDL-C, apolipoprotein Apo B, triglyceride, and low-density lipoprotein Lp (1) levels, age group, and ASCVD "risk enhancers."
  - Reduced eGFR (<60 mL/min/1.73 m^2 not on dialysis) and albuminuria (eg, albumin-to-creatinine ratio [ACR] >30 mg/g) are independently associated with elevated ASCVD risk.
  - ASCVD risk enhancers: chronic inflammatory conditions, history of preeclampsia, early menopause, South Asian ancestry, CKD, and HIV/AIDS (acquired immunodeficiency syndrome)
  - Reassess fasting lipid panel in 4 to 12 weeks after statin initiation to assess for adherence, dose adjustment, and adverse effects. Monitor

every 3 to 12 months as needed to assess adherence or safety.

- Consider *non-statin therapy* for those not tolerating statin or at high ASCVD risk despite maximal tolerable statin dose.
  - Bile acid sequestrants
  - Fibrates (may increase SCr due to increased metabolic production rate of creatinine or direct action on kidneys)
  - Nicotinic acid
  - Ezetimibe (limited vascular and clinical benefits)
  - Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors
  - Lipid apheresis

Hypercoagulability and thrombosis

- Highest risk during the first 6 months of diagnosis
- Venous thrombotic complications are much greater than arterial.
- Most common in membranous nephropathy
- Full-dose anticoagulation is required for 6 to 12 months and/or for the duration of the NS for the following: venous or arterial thrombosis, pulmonary embolism, nonvalvular atrial fibrillation
- Prophylactic full-dose anticoagulation should be considered for individuals with serum albumin less than 2 to 2.5 g/dL (<20-25 g/L) and one of the following thromboembolic risks:
  - Proteinuria greater than 10 g/d
  - Body mass index greater than 35 kg/m^2
  - Genetic disposition for thromboembolism
  - HF NYHA class III or IV
  - Recent orthopedic or abdominal surgery
  - Prolonged immobilization
- Relative or absolute contraindications for anticoagulation: patient preference/poor adherence, bleeding diathesis, hemorrhage prone CNS lesions, genetic indications influencing warfarin metabolism/efficacy, high fall risks, prior/ongoing GI bleed
- Anticoagulant selections for patients with membranous nephropathy and NS
  - For serum albumin less than 2.5 g/dL and high venous thromboembolic risk but with low bleeding risk, warfarin

anticoagulation is indicated. Target international normalized ratio should be 2 to 3. For ongoing thromboembolic events, heparin bridging should be added. Heparin dosing may be higher in patients with nephrotic syndrome to achieve target levels due to urinary loss of antithrombin III.

  - For serum albumin less than 3.2 g/dL (and ≥2.5 g/dL), and thromboembolic risk (based on Framingham risk score, estimated GFR, DM, previous arterial thromboembolism and additional risks due to NS) greater than 20 events/100 patient-years, the use of aspirin is suggested.
  - For serum albumin greater than 3.2 g/dL, no aspirin is needed.
- The use of direct oral anticoagulant (DOACs) and factor Xa inhibitors has not been systematically studied in patients with NS.
- An online tool to calculate bleeding risk versus benefits of anticoagulation in NS ("Prophylactic Anticoagulation in Patients With Membranous Nephropathy") is available on the University of North Carolina School of Medicine website (www.med.unc.edu/gntools/).

Risk of infection

- Vaccinations for patients with glomerular disease and NS
  - Pneumococcal vaccine
  - Herpes zoster (Shingrix)
  - Household contacts should receive the influenza vaccine.
- Screen for TB, hepatitis B and C, HIV, and syphilis in clinically appropriate patients.
- Strongyloides superinfection should be considered in patients receiving immunosuppressive therapy from endemic tropical regions who present with eosinophilia and elevated serum immunoglobulin E (IgE) levels.
- Prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (eg, rituximab, cyclophosphamide). Atovaquone or pentamidine may be substituted for those with sulfa-allergy.

Chronic Kidney Disease

Mechanisms of edema formation

- Volume overload is predominantly due to reduced glomerular filtration.
- Enhanced renal Na^+ reabsorption in patients with significant proteinuria may also contribute.

Management of volume overload in CKD

- Dietary sodium restriction to 2 to 2.5 g/d
- Use of diuretics:
  - Loop diuretics for volume overload
  - Thiazides are classified as weak diuretics. Chlorthalidone may still be effective as an antihypertensive agent and second-line diuretic even in CKD stage 4.
- For patients receiving dialysis who have edema who can still produce urine, increase diuretic dose as needed.

Advanced Liver Disease, Cirrhosis

Major hemodynamic changes induced by advanced liver disease, cirrhosis (Figure 1.8):

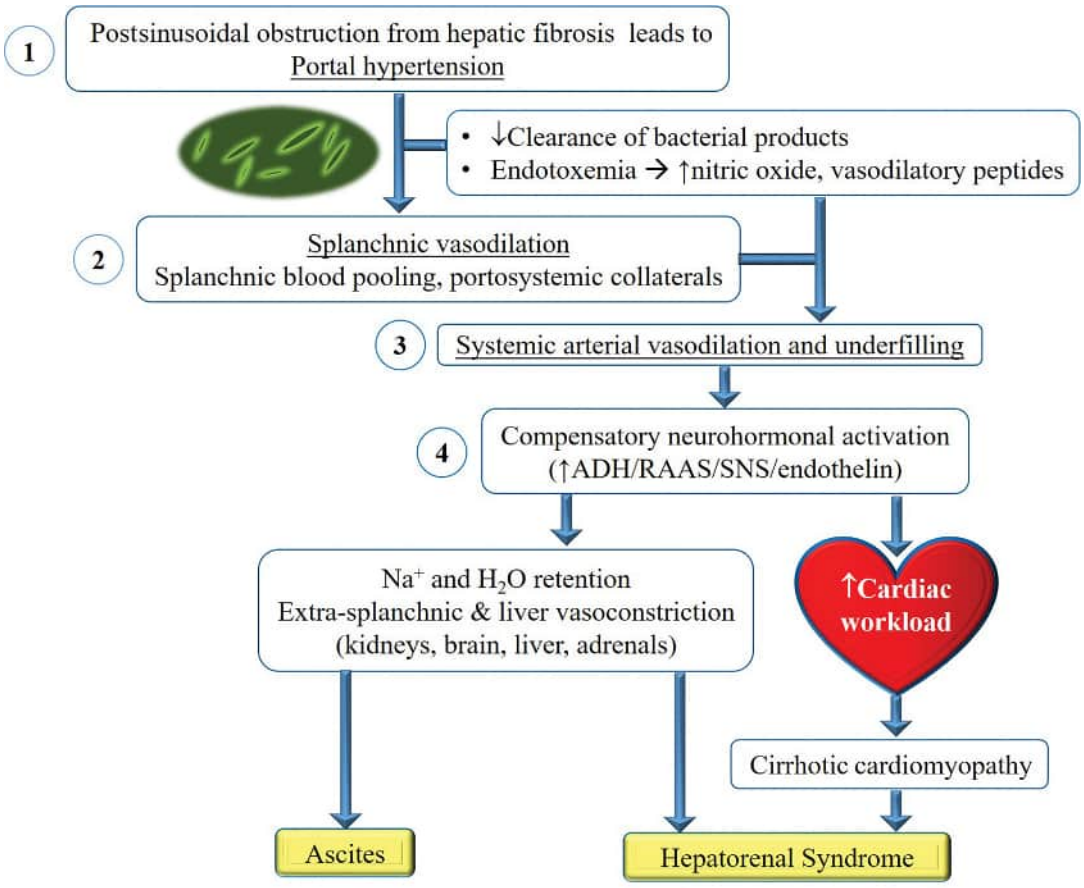


FIGURE 1.8 **Mechanisms of ascites formation and hepatorenal syndrome.** 1. Portal hypertension occurs because of postsinusoidal obstruction induced by hepatic fibrosis, followed by 2. splanchnic vasodilatation due to the local release of potent vasodilators and reduced clearance of bacterial products. 3. This in turn leads to splanchnic blood pooling, reduced systemic vascular resistance (from circulating splanchnic vasodilators), and fall in systemic effective circulating volume and blood pressure. 4. Compensatory neurohormonal activation promotes avid sodium and water reabsorption, increased cardiac workload, and systemic vasoconstriction (to offset the fall in systemic effective circulating volume and blood pressure), leading to ascites formation, cirrhotic cardiomyopathy, and hepatorenal syndrome.

Abbreviations: ADH, antidiuretic hormone; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

- ***Portal hypertension*** (pHTN) occurs as a result of postsinusoidal obstruction caused by hepatic fibrosis, followed by:
- Compensatory ***splanchnic vasodilation*** in response to local release of potent vasodilators (eg, nitric oxide, cannabinoids), a process thought to be driven by pHTN and reduced clearance of bacterial products. Splanchnic vasodilatation leads to splanchnic blood pooling and a fall in systemic effective circulating volume.

- Vasodilatory peptides escape metabolism by the cirrhotic liver, circulate systemically, and contribute to ***reduced systemic vascular resistance***.
- Hemodynamic alterations above lead to compensatory hyperdynamic cardiac output. With disease progression, cardiac dysfunction occurs, known as "cirrhotic cardiomyopathy."

Cirrhotic cardiomyopathy

- Cirrhotic cardiomyopathy (CCM) is characterized by cardiac chambers enlargement, reduced systolic and diastolic contractile response to stress stimuli, and repolarization changes.
- RAAS, SNS, and ADH systems are activated, and endothelin synthesis is increased.
- The incessant Na^+ and H_2O retention leads to edema and ascites formation.
- ADH leads to hyponatremia in the presence of excess-free water relative to solute intake.
- Severe vasoconstriction of renal arterial bed leads to a precipitous fall in glomerular filtration (GFR). This state of *functional* renal dysfunction is referred to as "hepatorenal syndrome."
- Management of CCM
- Currently, there is no specific pharmacologic therapy that can target CCM.
- Nonspecific management: diuretics, sodium and fluid restriction
- Afterload reduction in already low effective arterial volume can worsen hemodynamics.

Management of volume overload in cirrhosis

- Dietary sodium restriction to less than 2 g/d
- Use combination loop + MRA: for example, furosemide 40 to 160 mg/d + spironolactone 50 to 200 mg/d
- Titrate dose every 3 days to achieve net negative 1 L/d in patients with peripheral edema and 0.5 L/d in those without edema. More aggressive diuresis can cause AKI because only 0.3 to 0.5 L of ascitic fluid can be mobilized back into circulation via peritoneal capillaries daily.

- For patients with poor response to maximally tolerated diuretic dose (eg, net negative less than 1.5 L/wk), large-volume paracentesis (LVP) is indicated.
- For hospitalized patients, consider adding hyperoncotic albumin (eg, 25 g of 25% albumin bid-tid) for those with serum albumin less than 3 g/dL, to improve delivery of loop diuretics to the kidneys. The addition of salt-poor albumin has not been shown to increase sodium excretion in patients with NS or cirrhosis with mean serum albumin of 3 g/dL.
- Of interest, there is evidence suggesting that long-term albumin administration (40 g twice weekly for the first 2 weeks, followed by once weekly) in patients with decompensated cirrhosis reduces 18-month mortality and the incidence of complications and hospitalizations and eases the management of ascites.

Hepatorenal syndrome

Definition of HRS by the Ascites International Club

"HRS is a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure, and pHTN characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in a low GFR. In the extrarenal circulation, there is predominance of arterial vasodilation that results in reduction of total systemic vascular resistance and arterial hypotension."

Subtypes of HRS

- HRS-AKI (previously known as type 1 HRS): Increase in SCr by 0.3 mg/dL or more from stable baseline within 48 hours, or a 50% or more increase from baseline which is known, or presumed, to have occurred within the prior 7 days.
- HRS-CKD (previously known as type 2 HRS): The decline in GFR in HRS-CKD evolves over weeks to months (eGFR <60 mL/min/1.73 m^2 for ≥3 months).

Incidence: 18% at 1 year; 39% at 5 years
Prognosis: Renal function rarely spontaneously improves (<5%). Median survival without dialysis support for type 1 HRS: 2 weeks; type 2 HRS: 6

months.

NOTE

Criteria for the diagnosis of HRS based on the Ascites International Club

- Diagnosis of cirrhosis with ascites
- AKI as defined per AKIN/KDOQI:
  - Increase in SCr by 0.3 mg/dL or more from stable baseline in less than 48 hours OR
  - 50% or more increase from baseline which is known, or presumed, to have occurred within the prior 7 days.
- No improvement in SCr after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended albumin dose: 1 g/kg of body weight per day up to a maximum of 100 g/d)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs, no recent use of antibiotic or NSAIDs
- Absence of macroscopic kidney injury, that is, proteinuria less than 500 mg/d, microhematuria less than 50 red blood cells per high power field and normal renal ultrasonography

Preventive measures of HRS

- *Albumin infusion* is recommended for the following:
  - Initial presentation of kidney injury as volume expanding challenge: 1 g/kg/d up to 100 g/d for 48 hours or more
  - At diagnosis of spontaneous bacterial peritonitis (SBP): 1.5 g/kg at diagnosis and 1 g/kg IV 48 hours later
  - LVP greater than 5 L: 6 to 8 g/L of ascitic fluid removed

NOTE

- Patients without peripheral edema are at increased risk for circulatory collapse and development of AKI following LVP. The sudden drop in intra-abdominal pressure with LVP can favor increased splanchnic bed blood pooling, thus reduction of central venous blood return. The lack of peripheral edema, hence lack of interstitial fluid mobilization intravascularly to replenish the circulating volume, can lead to circulatory collapse and AKI.
- The infusion of hyperoncotic albumin in patients with cirrhosis who are volume depleted without any peripheral edema can precipitate AKI. The increased intracapillary oncotic pressure alone (without any added interstitial fluid mobilization into the intravascular space due to lack of peripheral edema) reduces the net filtration pressure needed to deliver oxygen and nutrients to renal tubules, thereby leading to ATN. Initial volume expansion with crystalloids or at maximum 5% (not 25%) albumin in these cases is warranted (authors' clinical observation and opinion).

- *Prophylactic antibiotic therapy* for spontaneous bacterial peritonitis (SBP) in at-risk individuals

> **FYI**
>
> Prophylactic antibiotic therapy for spontaneous bacterial peritonitis
> - Short-term prophylactic therapy:
> - Patients hospitalized for GI bleed (ceftriaxone 1 g/d); transition to oral quinolone or TMP-SMX bid × 7 days after stabilization
> - Patients hospitalized for other reasons with ascitic total protein less than 1 g/dL
> - Prolonged prophylactic therapy (quinolone or TMP-SMX DS daily):
> - Patients with one or more episode of SBP
> - Patients with cirrhosis and ascitic fluid total protein less than 10 g/L with Child-Pugh Score of greater than 9, serum bilirubin greater than 3 mg/dL, SCr greater than 1.2 mg/dL, BUN greater than 20 mg/dL, or S[Na^+] less than 130 mmol/L

- *Avoidance of nephrotoxins, NSAIDS, and overly aggressive diuresis*
- *Transjugular intrahepatic portosystemic shunts (TIPS):*
  - Divert portal blood flow to hepatic vein, thereby redistribute portal/splanchnic blood to central volume.
  - Improve variceal bleed and renal perfusion.
  - Complications: bleeding, infections, hepatic encephalopathy, renal failure
  - Typically, TIPS is not well-tolerated in patients with end-stage liver failure due to high risk for complications above (Child-Pugh class C).

Management of HRS

- *Vasoconstrictors:*
  - Improve short-term mortality (ie, 15 days) but not beyond.
  - The International Club of Ascites recommends the use of vasoconstrictors in patients with HRS stage 2 or 3 AKI.
  - Therapy with vasoconstrictors may be considered once HRS criteria are fulfilled, and no response observed over 48 hours following volume expansion with albumin.
  - Clinically available vasoconstrictors include continuous infusion of norepinephrine (NE) or AVP, IV bolus dosing of terlipressin, or oral midodrine + subcutaneous octreotide combination. See **Appendix A1.4** for dosing.

- US box warning: Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or those with acute-on-chronic liver failure Grade 3 are at increased risk. Assess oxygenation saturation before initiating terlipressin.

FYI

Efficacy studies among available vasoconstrictors:

- Systematic review and meta-analysis of 13 randomized controlled trials demonstrated equivalent reversal of HRS with terlipressin as it is with NE and albumin combination therapy.
- Systematic review and meta-analysis of 18 randomized controlled trials (n = 1,011) demonstrated that terlipressin was superior to placebo and octreotide for reversal of HRS (HRS reversal rate in terlipressin vs non-terlipressin group: 42% vs 26.2%, respectively).

- Predictors of response to vasopressors: baseline serum bilirubin level less than 10 mg/dL and increase in mean arterial pressure (MAP) of 5 mm Hg or more
- If there is a positive response, the effect will be apparent within 3 days. Therapy switch should be considered if there is no response to any selected agents above after 3 days (eg, failure to NE + albumin after 3 days should prompt a switch to AVP + albumin or terlipressin + albumin per availability) because not all patients will respond similarly to the same agent.

- *Liver transplantation:*
  - The only cure to end-stage liver disease. The incidence of end-stage kidney disease (ESKD) following liver transplantation is 7% in patients with HRS versus 2% in those without HRS.
  - Prioritization for liver allocation is based on UNOS MELD (United Network for Organ Sharing Model for End-Stage Liver Disease) Sodium Score in Liver Disease (**Appendix A1.5**).

See **Chapter 11: Acute Kidney Injury/ICU Nephrology,** for the diagnosis of AKI in the patient with cirrhosis.

Notable drug-induced edema

- Vasodilators: minoxidil (pericardial effusion and tamponade have been reported), diazoxide

- Thiazolidinedione-induced edema is thought to be due to: (1) increase in sodium reabsorption via ENaC and proximal tubules; (2) vascular vasodilation via activation of peroxisome proliferator-activated receptor γ (PPARγ) with subsequent fall in BP and resultant sodium retention: pioglitazone (rosiglitazone is discontinued from the market).
- Sex hormones (estrogen, testosterone) and antiandrogen (abiraterone): possibly via associated mineralocorticoid activity
- NSAIDs and cyclooxygenase-2 inhibitors (via reducing vasodilatory PGs in glomerular afferent arterioles thus GFR)
- Pramipexole, dopamine agonist, used to treat Parkinson disease and restless leg syndrome (suggested to be due to lymphatic insufficiency)
- Insulin (presumably via increasing aldosterone level and renal sodium reabsorption): Refeeding of individuals who fast for 3 or more days with carbohydrates may develop insulin-mediated sodium retention and edema, known as refeeding edema.
- See **Table 1.2** for more drug-induced edema.

Table 1.2 Drug-induced edema

↑Capillary hydraulic pressure Arteriolar vasodilatation	↑Capillary permeability, "capillary leak syndrome"	Lymphatic obstruction Anti-lymphangiogenic	Renal sodium and water retention
• Antidepressants (escitalopram, mirtazapine, paroxetine, venlafaxine) • Antihypertensives (minoxidil, hydralazine, calcium channel blockers) • Dopaminergic agonists (l-dopa, monoamine oxidase inhibitor) • Antipsychotics (clozapine, olanzapine, paliperidone, quetiapine,	• Anticancer (gemcitabine, pemetrexed, cyclophosphamide, clofarabine, all-transretinoic acid, taxanes [docetaxel, paclitaxel], ALK [ceritinib, crizotinib], BCR-Abl [imatinib, dasatinib, nilotinib, bosutinib, ponatinib], VEGF [sunitinib]) • Baclofen • Cytokines (granulocyte colony-stimulating	• Anticancer (taxanes [docetaxel, paclitaxel], PI3K/AKT [idelalisib, alpelisib]) • Tamoxifen • Mammalian target of rapamycin (everolimus, sirolimus)	• Antihypertensives (minoxidil, hydralazine) • Nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors • Corticosteroids • Diazoxide • Androgens (danazol, testosterone) Estrogens • Progestins • Aromatase inhibitors (anastrozole,

↑Capillary hydraulic pressure Arteriolar vasodilatation	↑Capillary permeability, "capillary leak syndrome"	Lymphatic obstruction Anti-lymphangiogenic	Renal sodium and water retention
risperidone, ziprasidone) • Diazoxide • Gabapentinoids (gabapentin, pregabalin) • Estrogens • Insulin • Prostaglandin I2 analogues/agonists (treprostinil, selexipag) • Endothelin receptor antagonists (ambrisentan, bosentan)	factor, interleukin 2, interferon-a2b) • Estrogens • Insulin • Prostaglandin I2 analogues/agonists (treprostinil, selexipag) • Endothelin receptor antagonists (ambrisentan, bosentan) • Calcineurin inhibitors (cyclosporine, tacrolimus) • Mammalian target of rapamycin (everolimus, sirolimus) • Opioids/analgesics (fentanyl, hydromorphone, morphine, oxycodone, tramadol) • Thymoglobulin		letrozole, exemestane) • Tamoxifen • Gonadotropin-releasing hormone agonists (goserelin, leuprolide) • Antiandrogen, abiraterone • Metapyrone • Insulin • Growth hormone • Endothelin receptor antagonists (ambrisentan, bosentan)

Note that there may be more than one mechanism for edema formation for many drugs.

Abbreviations: ALK, anaplastic lymphoma kinase; BCR-Abl, breakpoint cluster region, Abelson murine leukemia viral oncogene homolog; PI3K/AKT, phosphatidylinositol 3-kinase / protein kinase B; VEGF, vascular endothelial growth factor

Data from Largeau B, Cracowski JL, Lengellé C, Sautenet B, Jonville-Béra AP. Drug-induced peripheral oedema: an aetiology-based review. *Br J Clin Pharmacol*. 2021;87(8):3043-3055. doi:10.1111/bcp.14752

NOTE

- Dihydropyridine CCB-related peripheral edema is caused by the preferential precapillary arteriolar vasodilation relative to the venous bed, which leads to the transmission of the higher systemic pressure into the venous bed, resulting in an increase in hydraulic pressure within the venous bed, and subsequent fluid leak into the interstitial space and

edema formation. CCB-induced edema is NOT due to renal sodium retention. Management options for CCB-induced edema: compression stockings, leg elevation, and addition of agents with venodilating action such as ACEi, ARB, and nitrates per BP tolerability. Use of diuretics is ineffective in treating CCB-induced edema because this is not due to sodium retention. In addition, CCBs have been shown to have an intrinsic natriuretic effect.

- DPP4 inhibitor (sitagliptin) causing angioedema: DPP4 plays a significant role in the metabolism of bradykinin and substance P to their inactive metabolites. Patients with known angioedema with ACEi may be at risk for angioedema with DPP4 inhibitor.

SALT DEPLETION

Background

Salt-depleted state can arise from:

- CNS lesion (CSW)
- Lack of mineralocorticoid (eg, primary adrenal insufficiency, isolated aldosterone synthase deficiency [ASD], or loss-of-function mutation of mineralocorticoid receptor [renal pseudohypoaldosteronism])
- Kidneys' failure to reabsorb sodium (salt-wasting nephropathy, systemic pseudohypoaldosteronism [ENaC loss-of-function mutation], drug-induced renal salt wasting)
- GI fluid loss

Table 1.3 summarizes salt-depleted conditions.

Table 1.3 Salt-depleted conditions

	Specific conditions	Laboratory findings/diagnostic pearls	Management/comments
Brain	Cerebral salt wasting (CSW): associated with acute intracranial pathology, typically subarachnoid hemorrhage	• Laboratory findings are similar to those of SIADH. • Low serum uric acid; U_{OSM} >200-300 mosm/kg; $U[Na^+]$ >40 mmol/L • Low PRA and aldosterone levels	• Normal saline infusion or in severe cases, 3% saline • In contrast to patients with SIADH who are euvolemic, patients with CSW present with volume depletion and orthostatic hypotension. Volume repletion suppresses ADH and reduces U_{OSM}.

	Specific conditions	Laboratory findings/diagnostic pearls	Management/comments
Adrenals	Primary adrenal insufficiency (both glucocorticoid and mineralocorticoid deficiencies)	• Laboratory findings: hyperkalemia, hyponatremia, mild metabolic acidosis; High PRA, high aldosterone • Low blood pressure	• [a]Glucocorticoid (hydrocortisone or prednisone) • Fludrocortisone (0.05-0.2 mg/d) AND liberal sodium intake to maintain $U[Na^+]$ >20 mmol/L.
	Isolated aldosterone deficiency	• Laboratory findings: hyperkalemia, hyponatremia, metabolic acidosis; high PRA, low aldosterone	• Fludrocortisone (0.05-0.2 mg/d) AND liberal sodium intake to maintain $U[Na^+]$ >20 mmol/L
	Aldosterone receptor loss-of-function mutation (pseudohypoaldosteronism type 1 [PHA1], renal PHA1)	• Hypovolemia, sodium wasting, and hyperkalemia in neonatal period • Laboratory findings: hyponatremia, hyperkalemia, metabolic acidosis; very high PRA, plasma and urine aldosterone	• High salt diet ± Fludrocortisone 1-2 mg/d (or carbenoxolone) • Renal PHA1 improves well with salt supplement. Systemic PHA1 requires more aggressive therapy.
Kidneys	Salt-losing nephropathy	• Chronic kidney disease, tubulointerstitial diseases, pRTA, proteinuria	• Correct underlying renal disease. • Na^+ and K^+ supplement as needed.
	Epithelial sodium channel mutation (systemic PHA1)	• Laboratory findings are similar to renal PHA1 above. • Presentation of systemic PHA1 is more severe than renal PHA1 because ENaC	• Treat as renal PHA1; indomethacin may be considered to reduce urine output. • Associated complications include chronic pulmonary syndrome, cholelithiasis,

	Specific conditions	Laboratory findings/diagnostic pearls	Management/comments
		mutation affects multiple organs.	polyhydramnios, characteristic skin changes.
	Drug-induced kidney injury (cisplatin, tenofovir)	• Moderate-to-severe renal salt wasting; May be associated with Fanconi syndrome • May be complicated by ATN/ATI	• Preventive measure with normal saline infusion during cisplatin therapy is key.
	Postobstructive or post-ATN diuresis	Multiple etiologies possible—see text	Replace with oral or IVF as needed.
	Diuretic, osmotic agents	Review medical history	
GI	Emesis, biliary drains, diarrhea	See Chapter 2: Acid-Base and Potassium Disorders	Treat underlying condition.

[a]Hydrocortisone 20 mg and prednisone 50 mg provide a mineralocorticoid effect equivalent to approximately 0.1 mg of fludrocortisone. Addition of fludrocortisone may not be necessary in primary adrenal insufficiency.

Abbreviations: ADH, antidiuretic hormone; ATN/ATI, acute tubular necrosis/acute tubular injury; GI, gastrointestinal tract; IVF, intravenous fluids; PRA, plasma renin activity; pRTA, proximal renal tubular acidosis; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; U_{OSM}, urine osmolality; U_{Na}, urine sodium.

Cerebral Salt Wasting

- CSW is typically associated with subarachnoid hemorrhage but it has also been described with other forms of brain injuries.
- Suggested mechanisms:
  - Impaired sympathetic neural input leading to abnormal proximal tubular Na^+, uric acid, and water excretion and reduced renin release
  - Increased brain natriuretic peptide production
- Clinical manifestations: volume depletion, orthostatic hypotension

- Laboratory findings: hyponatremia, low serum uric acid, high urine osmolality, $U[Na^+]$ of much greater than 20 to 30 mmol/L, low renin and aldosterone levels (similar to those seen with SIADH)
- Treatment:
  - Volume repletion (normal saline, salt tablets if hemodynamically stable and can tolerate oral intake)
  - Consider mineralocorticoids, for example, fludrocortisone 0.2 mg twice daily.
  - CSW is typically a transient condition—long-term treatment is likely not necessary.

NOTE

- Common features between SIADH and CSW: high ADH and natriuretic peptide levels, high $U[Na^+]$, **low** renin and aldosterone levels, and low uric acid levels. ADH level decreases after volume repletion in CSW but not in SIADH.
- Difference between CSW and SIADH: Patients with CSW present with volume depletion, in contrast to patients with SIADH who present with euvolemia or mild hypervolemia. Normal saline infusion may worsen hyponatremia in SIADH when urine osmolality greater than 300 mOsm/kg but would improve hyponatremia in CSW. Accordingly, U_{OSM} can decrease with volume repletion in CSW.

Mineralocorticoid Deficiency

Causes of mineralocorticoid deficiency

- Primary adrenal insufficiency
- Isolated deficiency of aldosterone synthase activity
- Mineralocorticoid receptor resistance to aldosterone
- Drug-induced (eg., heparin, mineralocorticoid receptor antagonists)

Diagnostic testing of mineralocorticoid deficiency

The causes of mineralocorticoid deficiency can be differentiated by measurements of plasma renin activity (PRA), serum aldosterone, and serum cortisol. These levels are best measured following the administration of a loop diuretic or 3 hours after being in the upright position.

- Primary adrenal insufficiency (high PRA, low aldosterone, and low cortisol [high adrenocorticotropin hormone, ACTH])

- Isolated deficiency of aldosterone synthase activity (high PRA and low aldosterone)
- Mineralocorticoid receptor resistance to aldosterone (very high PRA and aldosterone)
- Drug induced (depends on the level of inhibition, ie, inhibition of aldosterone synthesis vs mineralocorticoid receptor)

Primary adrenal insufficiency

Underlying causes of primary adrenal insufficiency

- Congenital adrenal hypoplasia, adrenoleukodystrophy, autoimmune, infiltrative, and infectious diseases (HIV, TB, disseminated fungal infection, syphilis, African trypanosomiasis), metastatic malignancy, bilateral adrenalectomy, or hemorrhage
- Medication induced adrenal insufficiency: anticancer checkpoint inhibitors (CTLA-4 and PD-1), inhibitors of the RAAS, inhibitors of cortisol biosynthesis (etomidate, ketoconazole, fluconazole, metyrapone, antiparasitic suramin), both unfractionated and fractionated low-molecular-weight heparin (inhibit aldosterone synthesis and reduce Ang II level and affinity to its receptors in the zona glomerulosa), drugs that accelerate cortisol metabolism (phenytoin, barbiturates, rifampin), mitotane

Laboratory findings

- Varying degrees of hyponatremia, hyperkalemia, and metabolic acidosis
- ↑PRA, ↓aldosterone, followed by low cortisol in response to corticotropin (ACTH), then eventual ↓cortisol and high ACTH

NOTE

Secondary adrenal insufficiency due to pituitary disorders (affecting ACTH secretion) and tertiary adrenal insufficiency due to hypothalamic disorders (affecting corticotropin release hormone secretion) only present with hypocortisolism, NOT mineralocorticoid insufficiency. For this reason, both secondary and tertiary forms of adrenal insufficiency are not associated with hyperkalemia.

Management

- Glucocorticoid (hydrocortisone or prednisone) to correct cortisol deficiency

- Hydrocortisone 20 mg and prednisone 50 mg provide a mineralocorticoid effect equivalent to approximately 0.1 mg of fludrocortisone. The addition of fludrocortisone may not be necessary in primary adrenal insufficiency.
- Fludrocortisone (0.05-0.2 mg/d) may be added to increase sodium retention if hydrocortisone alone does not provide adequate mineralocorticoid activity.
- In patients with volume expansion and/or preexisting HTN, consider adding low dose loop or thiazide diuretics. This will not only reduce Na^+ retention but will also enhance distal Na^+ delivery for optimal fludrocortisone activity.

NOTE

Fludrocortisone requires tubular sodium delivery to cortical collecting tubules to work. Patients who are salt depleted cannot deliver adequate sodium to cortical collecting tubules, rendering fludrocortisone ineffective. That is, if a patient does not adequately respond to fludrocortisone (ie, persistent hyperkalemia ± hypotension), make sure the patient has adequate sodium intake, that is, U[Na^+] should be greater than 20 mmol/L, before increasing fludrocortisone dose.

Isolated aldosterone synthase deficiency

This is a rare autosomal recessive condition with a loss-of-function mutation in the gene CYP11B2 coding aldosterone synthase. This enzyme catalyzes the final three steps in aldosterone biosynthesis. Mutations involving CYP11B2 may affect either the hydroxylation of corticosterone at 18-carbon (ASD type 1) or the oxidation of 18-hydroxycorticosterone (ASD type 2). See **Figure 1.9**.

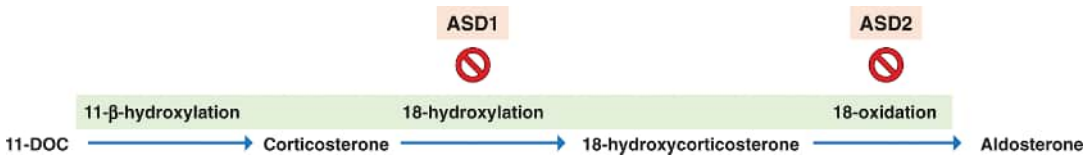


FIGURE 1.9 Aldosterone synthase deficiency. ASD1 involves a defect in the 18-hydroxylation of corticosterone to form 18-hydroxycorticosterone which results in a low level of 18-hydroxycorticosterone. ASD2 involves a defect in the 18-oxidation of 18-hydroxycorticosterone to form aldosterone which results in a markedly elevated level of 18-hydroxycorticosterone. Both ASD1 and ASD2 result in low levels of aldosterone and elevated plasma renin activity levels.
Abbreviations: ASD, aldosterone synthase deficiency; DOC, deoxycorticosterone.

Clinical manifestations: severe dehydration, vomiting, failure to thrive, hyperkalemia, and hyponatremia in infancy
Laboratory findings: hyperkalemia, hyponatremia, metabolic acidosis, increased PRA, low aldosterone
Management: salt replacement, fludrocortisone (0.05-0.2 mg/d)

(Renal) Pseudohypoaldosteronism type 1

A rare group of disorders characterized by resistance to aldosterone action is diagnosed in the neonatal period.

Renal type 1, autosomal dominant

- Defect: loss-of-function mutation of aldosterone receptor
- Clinical manifestations: milder salt wasting compared to systemic type 1 (see below), improves with age
- Treatment: high sodium supplementation ± fludrocortisone 1 to 2 mg/d or carbenoloxone (antagonizes cortisol metabolism thereby allowing accumulation of cortisol to activate mineralocorticoid receptors). Note that a much higher dose of fludrocortisone is needed in pseudohypoaldosteronism type 1 (PHA1) than that in primary adrenal insufficiency.

Systemic type 1, autosomal recessive

- Defect: loss-of-function mutation of ENaC
- Clinical manifestations: Salt-wasting presentation is typically much more severe because the ENaC mutation affects multiple organs. Associated complications are notable for chronic pulmonary syndrome (recurrent chronic coughs and wheezing, increased susceptibility to pulmonary infections), cholelithiasis, polyhydramnios, and characteristic skin changes.
- Treatment: high sodium supplementation; indomethacin may be considered to reduce urine output.

Laboratory findings common to both PHA1 types: hyperkalemia, hyponatremia, metabolic acidosis, significantly elevated renin and aldosterone levels. In systemic type 1, sweat chloride testing is also positive for high chloride secretion greater than 30 mmol/L.

Renal Salt Wasting

Salt-losing nephropathy

- Salt wasting may be observed in patients with advanced kidney disease, tubulointerstitial diseases, or proximal renal tubular acidosis (pRTA).
- Salt wasting in pRTA is due to obligatory Na^+ and K^+ losses associated with bicarbonaturia. Potassium loss also occurs due to volume depletion-induced increase in aldosterone.

Postobstructive diuresis

Contributing factors:

- Following the resolution of urinary obstruction, there is accelerated excretion of sodium, urea, and water that were retained during the obstructive phase.
- Increased atrial natriuretic peptide that occurred during the obstructive phase
- Relative nDI due to injury of collecting tubules associated with obstruction
- Iatrogenic due to excess volume replacement

Management: Replace with either oral or IV fluids (typically ½ normal saline tonicity) as needed at 30% to 50% of urine output volume. In patients who can tolerate oral intake, encourage oral fluid intake as safely tolerated to avoid iatrogenic polyuria caused by excessive IV fluid infusion.

Post-AKI diuresis

Contributing factors:

- Following the resolution of AKI, there is accelerated excretion of sodium, urea, and water retained during AKI.
- Increased atrial natriuretic peptide that occurred with fluid accumulation during AKI
- Delayed recovery of tubular function relative to glomerular filtration
- Iatrogenic due to excess volume replacement

Management: same as above for postobstructive diuresis; discontinue diuretics used during the AKI phase if applicable.

Drug-Induced Renal Salt Wasting

- Cisplatin, and to a lesser extent, carboplatin, may induce severe renal salt wasting in association with Fanconi syndrome. Prophylactic normal

saline infusion along with cisplatin administration is key.

- Tenofovir may also induce renal salt wasting in association with Fanconi syndrome and ATN.
- Diuretics

Diuretics

Background

- Traditional diuretics include carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics, ENaCi, and MRA.
- Sulfonamides contain the $-SO_2NH_2$ group and include carbonic anhydrase inhibitors, thiazide/thiazide-like diuretics, and loop diuretics.
  - Sulfonamides are 90% to 99% albumin-bound anions that are taken up by proximal tubules by organic anion transporters, then secreted into tubular lumen via the multidrug resistance-associated protein 4 (MRP4).
  - Allergic reactions to sulfonamides likely result from generalized hypersensitivity rather than specific cross-reactivity to the sulfonamide group.
- SGLT2i are glucose-lowering agents that also have weak diuretic effects.
- Vaptans are V2 receptor antagonists that induce aquaresis.

Table 1.4 summarizes all classes of diuretics, SGLT2i, and aquaretics.

Table 1.4 Diuretics, SGLT2 inhibitors, and vaptans

Diuretics	Bioavailability	$t_{1/2}$ (h)	Comments
Loop diuretics	• Dose equivalent for bumetanide, furosemide, and torsemide: 1:40:20 • Adverse effects: hypotension, hypokalemia, metabolic alkalosis, CO_2 retention, hyperuricemia, ototoxicity		
Bumetanide	80%-100%	1	Metabolized by both kidneys and liver; less ototoxic than furosemide
Furosemide	50%-60%	1.5-2	Primarily metabolized by the kidneys

Diuretics	Bioavailability	$t_{1/2}$ (h)	Comments
Torsemide	70%-100%	3-4	Primarily metabolized by the liver
Thiazide and thiazide-like diuretics	• Added benefit: fracture risk reduction (consider in individuals with high risk for osteoporosis) • Adverse effects: hypokalemia, hyponatremia, hyperuricemia, hypomagnesemia, metabolic alkalosis, hyperglycemia (via hypokalemia-associated inhibition in pancreatic insulin release)		
Hydrochlorothiazide	65%-75%	6-15	
Chlorthalidone	60%-75%	48-72	Shown to be effective in patients with CKD G4
Indapamide	100%	14-18	
Metolazone	65%-90%	6-8	
ENaC inhibitors	• Add-on therapy in patients with severe proteinuria (see text) • Promotes calcium and magnesium reabsorption at collecting tubules		
Amiloride	50%	6-9	
Triamterene	50%	3-5	Triamterene requires hepatic activation to hydroxytriamterene.
Mineralocorticoid receptor antagonist	Add-on therapy to benefit cardiovascular outcomes and slowing diabetic and nondiabetic CKD.		
Spironolactone	90%-95%	1.4	Most significant antiandrogenic effects of all MRAs
Eplerenone	70%	4-6	
Finerenone	40%-45%	2-3	• Nonsteroidal MRA, most selective MRA inhibitor of all MRA antagonists • Lower hyperkalemic/antihypertensive effects compared to spironolactone • Greater cardiac antifibrotic effect compared to spironolactone
Carbonic anhydrase	• Add-on therapy for those who develop severe metabolic alkalosis with the use of loop diuretics		

Diuretics	Bioavailability	$t_{1/2}$ (h)	Comments
inhibitors (CAi)	• Adverse effects: hypocalcemia, hypomagnesemia, calcium phosphate stones, metabolic acidosis		
Acetazolamide	90%	4	Non-diuretics with CAI property: topiramate, lacosamide, zonisamide
Others			
SGLT2 inhibitors	• Benefits: slows diabetic and nondiabetic CKD progression; decreases risk of AKI, HF hospitalization, and cardiovascular mortality; associated uricosuric effect may be advantageous in patients with gout. • Adverse effects: genital and urinary tract infections, euglycemic diabetic ketoacidosis		
Vaptans	• Vasopressin antagonists to V2 receptors in collecting ducts: oral tolvaptan (V1) and IV conivaptan (V1, V2) • Adverse effects: hypernatremia, hypokalemia, ↑risk of GI/variceal bleeding in patients with liver disorder, transaminitis		

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ENaC, epithelial sodium channel; GI, gastrointestinal; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter 2; $t_{1/2}$, half-life; V1, V2, arginine vasopressin receptor 1 and 2.

Loop diuretics

- Most potent class of diuretic because 20% to 25% of filtered sodium load is reabsorbed at the thick ascending limb of the Henle loop.
- Loop diuretics disrupt TGF by inhibiting sodium-potassium 2-chloride cotransporter (NKCC) at macula densa, the chloride sensing mechanism required in TGF.
- Loop diuretics are primary agents for volume-overloaded states (HF, cirrhosis, NSs, kidney failure).
- Dose equivalent for bumetanide, furosemide, and torsemide: 1:40:20 (eg, 1 mg bumetanide = 40 mg furosemide = 20 mg torsemide)
- Adverse effects: hypotension (via volume depletion as well as vascular vasodilatory effect), hypokalemia, metabolic alkalosis with accompanying CO_2 retention (risk for CO_2 narcosis in chronic CO_2

retainers), hyperuricemia, ototoxicity. Hypernatremia is a possible complication.

Thiazide and thiazide-like diuretics (TZDs)

- TZDs may be used as add-on diuretic therapy with loop diuretics for more aggressive diuresis, particularly in "braking" phenomenon observed with chronic loop diuretic use. Braking phenomenon is thought to be due to avid sodium reabsorption throughout the nephron in response to activated RAAS (eg, in HF) and rapidly depleting volume with aggressive diuresis.
- Treatment of HTN: Thiazides are considered one of the first-line antihypertensive agents because they also have vasodilating effects (eg, chlorthalidone, indapamide).
- Added benefit: risk reduction of fractures (consider use in hypertensive women with high risk for osteoporosis)
- Adverse effects: hypokalemia, hyponatremia, hyperuricemia, hypomagnesemia, metabolic alkalosis, hyperglycemia (via hypokalemia-associated inhibition in pancreatic insulin release)

General points regarding TZDs

- Long-acting chlorthalidone and indapamide have been shown to reduce cardiovascular events in randomized trials. There are no similar data for short-acting hydrochlorothiazide (HCTZ). The use of long-acting agents is generally preferred over HCTZ in the treatment of HTN.
- However, a study involving 13,523 veterans with the mean age of 72 years revealed no cardiovascular outcome difference at a 2.4-year follow-up between chlorthalidone and HCTZ.
- BP reduction is significantly greater with chlorthalidone and indapamide compared with HCTZ.
- Adverse effects: hyponatremia, hypokalemia, hypercalcemia, hyperglycemia, hyperuricemia (gout risk), hypomagnesemia, hyperlipidemia (transient)
- Hypokalemia is thought to play a role in reducing pancreatic insulin secretion, thus thiazide-associated hyperglycemia. Thiazide-induced hyperglycemia may be minimized with the concurrent use of RAAS inhibitors or potassium supplements.

- Thiazides and thiazide-like diuretics may be added to loop diuretics to treat refractory edema.
- Among patients with advanced CKD and poorly controlled HTN, chlorthalidone therapy improved blood pressure control at 12 weeks as compared with placebo.
- Although metolazone has been reported to work even at GFR less than 20 mL/min/1.73 m^2, it may have been related to the use of a very high dose and not any intrinsic drug characteristic.

Differences between loop and thiazide/thiazide-like diuretics

- Antidiuretic activity duration is short lived (ie, <2 weeks) with thiazides due to increased compensatory sodium reabsorption at more proximal nephron segments.
- Calcium wasting is seen with loop while calcium sparing is seen with thiazides.
- Hyponatremia is commonly seen with thiazides but not with loop diuretics. In fact, excessive diuresis with loop diuretics can result in hypernatremia. For mechanism of thiazide-induced hyponatremia, please refer to **Appendix A1.6**.
- Of note, potassium depletion (eg, associated with diuretic use) may directly stimulate water intake via alterations in osmoreceptor sensitivity and increase thirst. This may play a contributory role in diuretic-induced hyponatremia.

ENaCi (amiloride, triamterene)

- ENaCi may be used as add-on diuretic therapy in patients with severe proteinuria to counteract ENaC activation by plasmin (produced from urinary loss of plasminogen along with proteinuria).
- May be used in patients with activated ENaC activity in Liddle syndrome
- These agents promote calcium and magnesium reabsorption at collecting tubules.

MRAs (spironolactone, eplerenone, finerenone)

- May be used as add-on medical therapy to benefit long-term cardiovascular outcomes and to slow both diabetic and nondiabetic CKD

- Commonly used in combination with loop diuretics in patients with cirrhosis to counteract the hypokalemic effect of loop diuretic and cirrhosis-associated activated RAAS
- Spironolactone is the most antiandrogenic agent of all MRAs.
- Finerenone is the most selective MRA.

Sodium-glucose cotransporter 2 inhibitors

- Glucose-lowering agent with anti-inflammatory and mild diuretic effects
- May cause a functional decline in GFR by restoring TGF, but preserve kidney function long term, presumably via a reduction in glomerular HTN
- Slow both diabetic and nondiabetic CKD progression.
- Decrease proteinuria.
- Decrease risk of AKI, HF hospitalization, and cardiovascular mortality.
- Consider dose reduction of loop diuretic when adding SGLT2i.
- Major adverse effects: genital and urinary tract infections, euglycemic diabetic ketoacidosis
- Uricosuric effect: may reduce risk of new-onset gout

Vaptans

- AVP antagonists to V2 receptors in collecting ducts
- Currently not included in the routine management of HF
- Drugs: oral tolvaptan (V2) and IV conivaptan (V1 and V2)
- Adverse effects: increased thirst, hypernatremia, hypokalemia, possible increased risk of GI/variceal bleeding in patients with liver disorder, transaminitis
- Maximum duration of use: 30 days due to concerns for GI bleed and transaminitis

Osmotic agents (eg, mannitol)

- Not used as a diuretic agent but for decreasing intracranial pressure—Hypertonic saline is now used in place of mannitol to decrease intracranial pressure.

- Risks: rapid intravascular expansion and associated pulmonary edema, hyponatremia (due to rapid extracellular water shift), hyperkalemia (rapid extracellular water shift with solvent drag effect, ie, K^+ gets "dragged" out with the extracellular water shift)

Gastrointestinal Losses

Clinical history

Gastric fluids, biliary drains, colonic fluids

Laboratory findings

- High U_{OSM}, low $U[Na^+]$ of less than 10 to 20 mmol/L
- Exceptions: $U[Na^+]$ may be greater than 20 mmol/L if there is concurrent kidney failure from ATN or acute vomiting.
- Vomiting: Metabolic alkalosis—See **Chapter 2: Acid-Base and Potassium Disorders** for changes in urinary electrolyte findings associated with vomiting.
- Diarrhea—Also see **Chapter 2: Acid-Base and Potassium Disorders.**
  - Acquired infectious or inflammatory bowel-associated diarrhea: normal anion gap metabolic acidosis with negative urine anion gap
  - Congenital chloridorrhea or villous adenoma: metabolic alkalosis, hypokalemia

POLYURIA

Background

- Polyuria is typically defined as having urine volume greater than 40 mL/kg body weight/d. For individuals with partial DI, the urine volume may be slightly lower. Example: For a 70-kg person, polyuria is having urine output greater than 70 × 40 = 2,400 mL/d.
- Polyuria may be due to osmotic diuresis, aquaresis, or both.

Osmotic Diuresis

- Osmotic diuresis may be diagnosed when total daily osmolar output in the urine significantly exceeds the average daily dietary osmolar input.

For an average American dietary intake, the daily osmolar input is approximately 10 mOsm/kg body weight.

Example: A 70-kg individual with a urine osmolality of 300 mOsm/kg and total urine volume of 3.5 L/d (assuming adequate urine collection)

- For this 70-kg individual, normal urine output should not exceed 70 kg × 40 mL/kg = 2.8 L. A urine output of 3.5 L/d is consistent with polyuria.
- Total urine osmolar output = urine osmolality × total urine volume = 300 mOsm/kg × 3.5 L = 1,050 mOsm. This is significantly greater than the expected daily solute intake of 10 mOsm/kg/d for this 70-kg individual, which is 10 mOsm/kg × 70 kg = 700 mOsm. The high urine osmolar output suggests the presence of osmotic diuresis.
- Common causes of osmotic diuresis: hyperglycemia (eg, poorly controlled diabetes or use of SGLT2i), urea (eg, urea retained during AKI that gets excreted during AKI recovery phase as post-AKI diuresis, hypercatabolism with glucocorticoid use), mannitol, total parenteral nutrition, or just very high dietary protein intake compared with an average intake for the population, excessive saline infusion

Aquaresis

Normal renal H_2O reabsorption

- The differential diagnosis for aquaresis may be categorized based on the basic steps involved in how free water is normally reabsorbed by the kidneys (**Figure 1.10**).

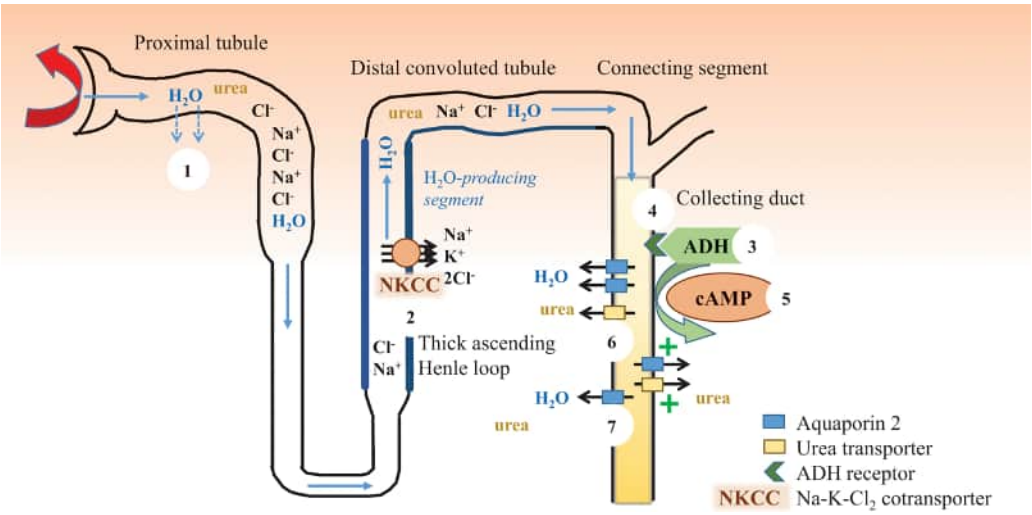


FIGURE 1.10 Water reabsorption within a nephron segment. 1. Water is reabsorbed passively at the proximal tubule. **2.** Free water is produced within the lumen of the water impermeable thick ascending Henle loop when $Na^+/K^+/2Cl$-gets reabsorbed via NKCC. **3.** In the presence of ADH and binding of ADH to **4.** its receptor, **5.** cAMP is produced which mediates the increase in the expression of both aquaporin 2 and urea transporters. **6.** Increased urea transport from the lumen increases the medullary tonicity which serves to reabsorb water from the collectingduct via aquaporin 2. **7.** Intact aquaporin 2 is needed for free water reabsorption.
Abbreviations: ADH, antidiuretic hormone; cAMP, cyclic adenosine monophosphate.

- Any interference with normal H_2O reabsorption can lead to aquaresis.

FYI

Normal free water reabsorption occurs as follows:

- Following glomerular filtration, salt and water are delivered to the thick ascending limb of the loop of Henle and distal convoluted tubules (DCT).
- At these nephron segments where there is relative impermeability to H_2O (more so in the loop of Henle than DCT), intraluminal free H_2O is "produced" when sodium chloride is reabsorbed but not H_2O.
- Free H_2O "produced" is delivered to the collecting tubules where it can be reabsorbed via apical AQP2, and basolateral AQPs 3 and 4. The efficiency of H_2O reabsorption depends on the presence and integrity of AQP2 and a high medullary concentration gradient (high tonicity). The latter acts as a dry sponge which soaks up any H_2O delivered to collecting tubules: The higher the medullary concentration gradient, the more efficient the H_2O reabsorption.
- AQP2 regulation via ADH: ADH binds to its receptor and activates adenylyl cyclase via G-protein to produce cAMP. cAMP mediates the shuttling of cytoplasmic AQP2 to the apical side of principal cells along the collecting tubules where intraluminal H_2O can be reabsorbed. Prolonged ADH elevation (>24 hours) can also increase the expression of AQP2.
- ADH also stimulates the shuttling of urea transporters to cell surfaces in the inner medullary collecting ducts to increase urea reabsorption, thereby enhancing the inner medullary tonicity required for optimal water reabsorption.

Aquaresis occurs when there is any problem associated with any step required for normal effective H_2O reabsorption (Table 1.5):

Table 1.5 Limitations for effective water reabsorption and associated conditions

Refer to Figure 1.10	Problems leading to suboptimal H_2O reabsorption	Conditions
1	Proximal tubular dysfunction	Poor proximal tubular function
2	Suboptimal NKCC cotransporter	Hypokalemia, hypercalcemia
3	Reduced ADH level	Reduced ADH synthesis (central diabetes insipidus), pregnancy-associated increase in vasopressinase production
4	Abnormal ADH receptor	X-linked mutation of ADH receptor
5	Reduced cAMP production	Hypokalemia, hypercalcemia, demeclocycline, lithium
6	Reduced medullary concentration/tonicity	Sickle cell disease, malnutrition, suboptimal NKCC function
7	Reduced AQP2 function or expression	Autosomal dominant or recessive mutation of AQP2 Downregulation of AQP2: hypokalemia, malnutrition, lithium

Abbreviations: ADH, antidiuretic hormone; AQP2, aquaporin 2; cAMP, cyclic adenosine monophosphate; NKCC, sodium-potassium 2-chloride cotransporter.

- Increased distal salt and water delivery: primary polydipsia, IV fluid infusion
- Reduced ADH level:
  - Reduced production: cDI
  - Increased metabolism: gestational DI where there is increased placental vasopressinase production, an enzyme that breaks down ADH
- Abnormal ADH (AVP) receptor: nDI due to loss-of-function mutation of AVP receptor
- Defect in cAMP production: chronic poor kidney function, hypokalemia, hypercalcemia, demeclocycline, lithium
- Problems with AQP2:
  - Mutation of AQP2 with functional defect

    - Downregulation of AQP2: chronic poor kidney function, hypokalemia, malnutrition, lithium therapy
- Loss of medullary concentration gradient: chronic poor kidney function, hypokalemia, hypercalcemia, sickle cell disease, protein malnutrition, chronic polydipsia, lithium

Specific Conditions With Aquaresis

Primary polydipsia

- Patients with psychiatric illness or anxiety disorders
- Medication-induced polydipsia: high-dose antihistamines, decongestants, anticholinergics, urinary incontinence drugs (oxybutynin), antidepressants, psycholeptics
- Hypothalamic lesions affecting the thirst center (sarcoidosis)

Central diabetes insipidus

Idiopathic (autoimmune injury to ADH-producing cells): These patients can present with the lack of hyperintense T1 signal within the posterior pituitary on brain MRI.
Trauma, neurosurgery: Although rare, triphasic response may be observed with severe hypothalamic or hypothalamic tract injury.

- Hypothalamic shock: During the initial hypothalamic shock phase, beginning within 24 hours and lasting up to 4 to 5 days, polyuria occurs because ADH release is inhibited.
- Antidiuretic phase: During the second phase, days 6 to 11, there is a slow release of stored ADH from the degenerating posterior pituitary. This stage is equivalent to SIADH. Excess-free water intake can cause hyponatremia.
- Permanent cDI: This last phase is due to depletion of stored ADH in the posterior pituitary.

Pituitary surgery
Hypoxic/ischemic encephalopathy
Malignancy (metastatic disease involving hypothalamic-pituitary region, particularly lung, leukemia, lymphoma, craniopharyngioma, pinealoma)
Familial (rare, autosomal dominant; due to preservation of function of the normal allele, polyuria may not present until after the first year of life or even in young adulthood)

Infiltrative diseases

- Langerhans cell histiocytosis aka histiocytosis X: rare histiocytic disorderly commonly characterized by single or multiple osteolytic bone lesions with histiocytes infiltration; extraskeletal involvement: skin, lymph nodes, lungs, thymus, liver, spleen, bone marrow, CNS
- Granulomatous diseases: sarcoidosis, TB, granulomatosis polyangiitis
- Autoimmune lymphocytic hypophysitis: lymphocytic infiltration and enlargement of the pituitary followed by destruction of pituitary cells. More common in women, often associated with late pregnancy or postpartum
- Immunoglobulin G4-related disease (IgG4-related disease)

Post-supraventricular tachycardia: due to decreased ADH secretion, presumably due to increased left atrial and systemic pressure and subsequent activation of local baroreceptors

Other causes of cDI: cerebral aneurysm, anorexia nervosa, infections, Guillain-Barré

Nephrogenic diabetes insipidus

Hereditary nDI

- Severe polyuria and hypernatremia typically occur during the first week of life.
- X-linked: mutations of AVPR2 gene encoding the AVP V2R
- Autosomal recessive and dominant: mutations of AQP2 gene

Acquired nDI

- Drug induced: lithium, demeclocycline
- Electrolyte disturbances: hypercalcemia, hypokalemia
- Conditions leading to reduced medullary concentration gradient: sickle cell disease/trait, protein malnutrition

Gestational diabetes insipidus

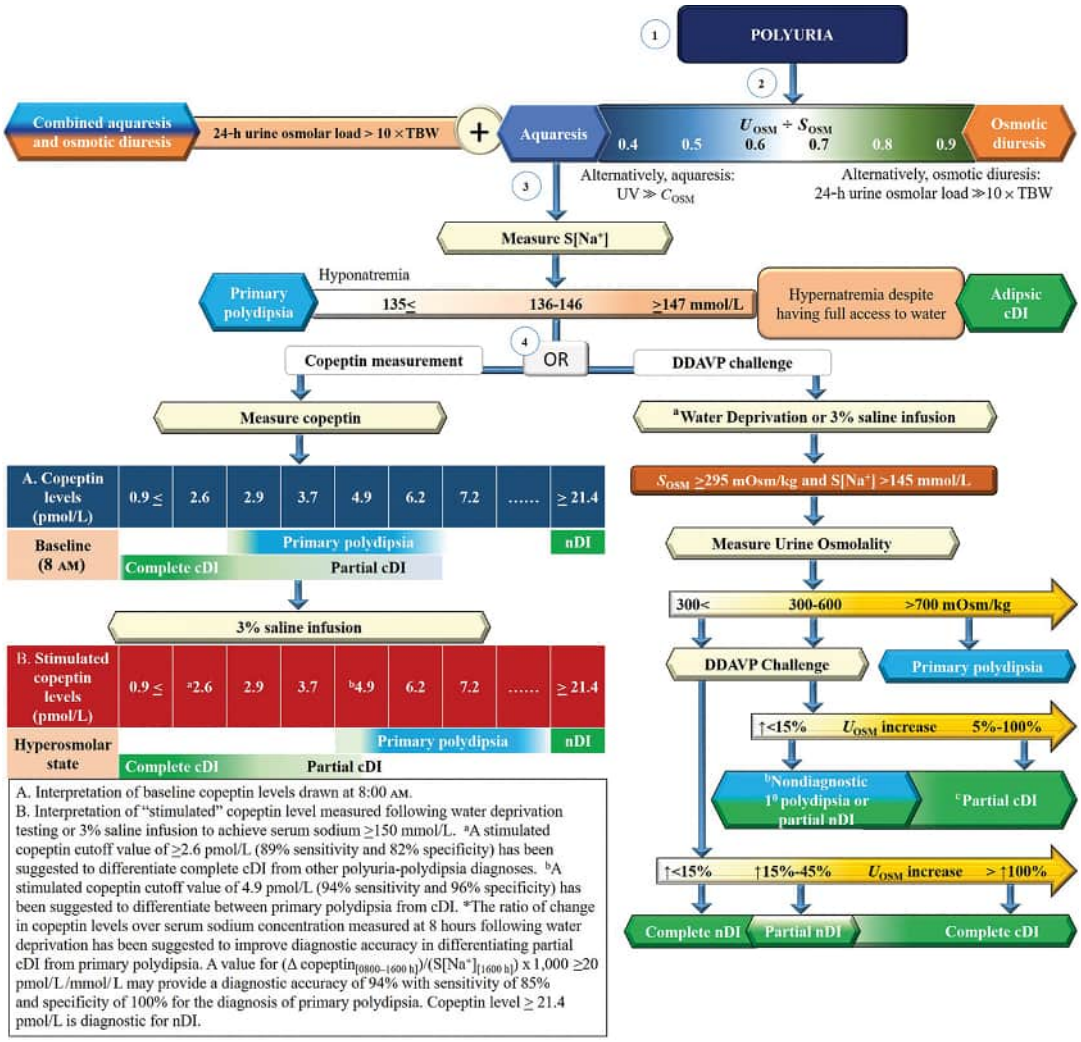
- In the setting of pregnancy with twins or triplets or large placental weight, pregnancy complicated by the **H**emolysis **E**levated **L**iver enzyme and **L**ow **P**latelet (HELLP) syndrome or preeclampsia, or subclinical cDI, a transient DI may occur due to placental production of vasopressinase.

- This condition may be treated with desmopressin acetate (DDAVP) but not AVP (Pitressin). Vasopressinase breaks down AVP (Pitressin) and renders it inactive but not DDAVP. cDI would respond to either DDAVP or Pitressin, but gestational DI due to increased vasopressinase level only responds to DDAVP. Gestational DI resolves with delivery.

NOTE

- In adults, the onset of cDI is usually abrupt, that is, patients can pinpoint the onset of disease, whereas the onset of acquired nDI or primary polydipsia is typically gradual.
- New-onset nocturia may be an early sign of newly developed DI (ie, nocturnal need to urinate despite cessation of fluid intake).

Diagnosing polyuria (Figure 1.11)



A. Interpretation of baseline copeptin levels drawn at 8:00 AM.
B. Interpretation of "stimulated" copeptin level measured following water deprivation testing or 3% saline infusion to achieve serum sodium ≥150 mmol/L. [a]A stimulated copeptin cutoff value of ≥2.6 pmol/L (89% sensitivity and 82% specificity) has been suggested to differentiate complete cDI from other polyuria-polydipsia diagnoses. [b]A stimulated copeptin cutoff value of 4.9 pmol/L (94% sensitivity and 96% specificity) has been suggested to differentiate between primary polydipsia from cDI. *The ratio of change in copeptin levels over serum sodium concentration measured at 8 hours following water deprivation has been suggested to improve diagnostic accuracy in differentiating partial cDI from primary polydipsia. A value for $(\Delta \text{ copeptin}_{(0800-1600\ h)})/(S[Na^+]_{(1600\ h)}) \times 1{,}000$ ≥20 pmol/L/mmol/L may provide a diagnostic accuracy of 94% with sensitivity of 85% and specificity of 100% for the diagnosis of primary polydipsia. Copeptin level ≥ 21.4 pmol/L is diagnostic for nDI.

FIGURE 1.11 Evaluation of polyuria. Step 1: Confirm polyuria (typically >40 mL/kg/d urine output, but may be less, particularly among patients with partial diabetes insipidus). Step 2: Determine the presence of aquaresis, osmotic diuresis, or both. Step 3: Measure $S[Na^+]$ to rule out primary polydipsia or adipsic cDI. Step 4: Either perform traditional water deprivation testing with DDAVP challenge or with copeptin measurements to determine complete or partial cDI, nDI, or primary polydipsia.

Abbreviations: 1° polydipsia, primary polydipsia; cDI, central diabetes insipidus; C_{OSM}, osmolar-free water clearance; DDAVP, desmopressin; nDI, nephrogenic diabetes insipidus; $S[Na^+]$, serum sodium concentration; S_{OSM}, serum osmolality; TBW, total body weight (kg); U_{OSM}, urine osmolality; UV, urine volume.

[a]Water deprivation or 3% saline infusion is not needed if a patient presents with $S[Na^+]$ ≥145 mEq/L and S_{OSM} ≥295 mOsm/kg.

[b]Nondiagnostic: Provide 3-day trial of desmopressin at 10 µg intranasally once daily for 3 days along with fluid restriction to 1.5 to 2.0 L/d. If thirst persists and hyponatremia develops, the diagnosis is primary polydipsia. If thirst and polyuria resolve, the diagnosis is partial central DI. Close monitoring is required during this test.

[c]Partial cDI may have sufficient endogenous ADH secretion with water deprivation and hyperresponsiveness to the small ADH increase due to presumed the upregulation of ADH receptors. The addition of DDAVP may not further concentrate the urine. This scenario could be mistaken as primary polydipsia. Clinical history of sudden onset, however, would favor cDI over polydipsia.

Confirm polyuria: Rule out urinary frequency: Confirm urine volume is approximately equal to or greater than 40 mL/kg/d.

Determine the type of polyuria: aquaresis, osmotic diuresis, or both

Osmotic diuresis is likely if:

- Total urine osmolar load (24-hour urine volume × U_{OSM}) is much greater than 10 × total body weight (kg).
- On an average American diet, urine osmolar load is approximately 10 mOsm/kg body weight.

Aquaresis is likely if:

- Urine volume × (1 − U_{OSM}/S_{OSM}) is much greater than 0 or urine volume is much greater than C_{OSM}.
- Alternatively, having polyuria with U_{OSM} (obtained from a timed urine collection, ie, 24-hour urine collection) lower than S_{OSM} indicates aquaresis.

- The presence of aquaresis may reflect the excretion of excess-free water intake relative to solute intake or any form of DI.

Combined osmotic diuresis and aquaresis are likely if:

- Urine osmolar load of greater than 10 mOsm/kg × total body weight (kg)
  AND
- Large osmolar-FWC, that is, urine volume × (1 − U_{OSM}/S_{OSM}) is much greater than 0, or
  - Urine volume is much greater than C_{OSM}, or
  - U_{OSM} from a timed urine collection is lower than S_{OSM}, typically, U_{OSM}/S_{OSM} ratio less than 0.7.

If aquaresis is present, determine the underlying etiology (primary polydipsia, cDI, nDI)

- Based on presenting $S[Na^+]$, a diagnosis may be made without further testing for the following:
  - Low U_{OSM}, normal or low total urine osmolar load, and low $S[Na^+]$ at presentation: Diagnosis of primary polydipsia is likely.
  - Adult patients with thirst sensation defect and $S[Na^+]$ greater than 145 mmol/L despite unlimited water access: Diagnosis of adipsic DI is likely.
  - U_{OSM} is much lower than S_{OSM} and $S[Na^+]$ greater than 145 mmol/L in infants/children with a family history of nDI: Diagnosis of nDI is likely. Consider genetic testing.
- If the underlying etiology of polyuria is not obvious or known, the diagnosis may be made by measuring baseline and stimulated copeptin levels or performing the traditional water deprivation test with the DDAVP challenge (see **Figure 1.11**).

Measuring Copeptin

- Copeptin level of 21.4 pmol/L or more: Diagnosis is nephrogenic DI.
- For copeptin level of less than 21.4 pmol/L: 3% saline infusion may be given to increase $S[Na^+]$ to at least 150 mmol/L to maximize ADH secretion. In primary polydipsia, ADH secretion is expected to

maximally increase at $S[Na^+]$ of 150 mmol/L or more, that is, "stimulated" copeptin will increase, whereas in cDI, the copeptin level remains relatively unchanged. A stimulated copeptin cutoff value of 4.9 pmol/L (94% sensitivity and 96% specificity) has been suggested to differentiate between primary polydipsia from cDI.

Water deprivation testing with DDAVP challenge: There are two phases to this test.

Phase 1

- Aim of phase 1 is to induce a hyperosmolar state (S_{OSM} >295 mosm/kg and $S[Na^+]$ >145 mmol/L) to assess the concentrating ability of the kidneys. Hypertonic saline (0.05 mL/kg/min infusion for 2 hours or shorter duration) may be considered if water deprivation is not an option. If patient presents with S_{OSM} greater than 295 mosm/kg and $S[Na^+]$ greater than 145 mmol/L, water deprivation or hypertonic saline is not needed.
- If S_{OSM} is greater than 295 mosm/kg, $S[Na^+]$ is greater than 145 mmol/L, and U_{OSM} is 600-700 mosm/kg or greater, the underlying etiology for polyuria is likely primary polydipsia. In patients with primary polydipsia, where renal water reabsorption is suboptimal due to a "washed out medulla," hypernatremia can develop with strict water restriction.
- If the patient presents with S_{OSM} greater than 295 mosm/kg, $S[Na^+]$ greater than 145 mmol/L, and U_{OSM} lower than 700 mosm/kg, proceed directly to phase 2 DDAVP challenge.

Phase 2

- Once the patient has safely achieved the hyperosmolar goal of S_{OSM} of greater than 295 mOsm/kg and $S[Na^+]$ of greater than 145 mmol/L and U_{OSM} of less than 700 mOsm/kg, DDAVP is administered.
- Changes in U_{OSM} in response to DDAVP are recorded every 30 minutes for 2 hours.

Interpretation of water deprivation + DDAVP challenge

***U_{OSM}* of less than 300 mOsm/kg following phase 1** suggests the presence of either complete nDI or complete cDI. DDAVP challenge in phase 2 helps differentiate these two conditions.

- Complete cDI:
  - U_{OSM} increases greater than 100% from phase 1.
- Complete nDI:
  - U_{OSM} increases by less than 15% from phase 1.
  - Caveat: High ADH levels achieved during water deprivation/hypertonic saline infusion can partially overcome renal resistance to ADH, resulting in U_{OSM} of greater than 300 mOsm/kg.

***U_{OSM}* of greater than 300 up to 600 mOsm/kg following phase 1** suggests partial cDI, partial nDI, or primary polydipsia. DDAVP challenge in phase 2 helps differentiate these conditions.

- Partial cDI:
  - U_{OSM} increases by 15% to 100% from phase 1.
  - Note: Patients with partial cDI may have sufficient endogenous ADH secretion with water deprivation and hyperresponsiveness to the small ADH increase due to upregulation of ADH receptors. The addition of DDAVP may not further concentrate the urine. This scenario could be mistaken as primary polydipsia or nDI. Clinical history of sudden onset, however, would favor central DI over polydipsia or nDI.
- Nondiagnostic:
  - U_{OSM} following the DDAVP challenge increases by less than 15%.
  - Provide a 3-day trial of desmopressin 10 µg intranasally qd × 3 days: If thirst persists and hyponatremia develops, the diagnosis is primary polydipsia. If thirst and polyuria resolve, the diagnosis is partial nDI. Close monitoring of serum sodium is required.

Management of Polyuria

Management of polyuria depends on the underlying etiology. See **Table 1.6** for condition-specific management options.

Table 1.6 Management of polyuria

Conditions	Therapy

Polydipsia	• Avoid anticholinergic agents, antihistamines, decongestants
	• Behavioral therapy, patient education
	• [a]Medical therapy:
	  • Atypical antipsychotics (varying benefits for psychogenic polydipsia): clozapine, olanzapine
	  • Others: ACEi, ARB, clonidine, propranolol, acetazolamide

Adipsic diabetes insipidus	DDAVP
Central diabetes insipidus	DDAVP
Pregnancy-associated diabetes insipidus	DDAVP until delivery

Nephrogenic diabetes insipidus	• General nonspecific therapies:
	  • Low dose thiazide diuretic
	  • Low-sodium and low normal protein diet (nutrition consult suggested to prevent malnutrition)
	  • Specific therapies:
	• Lithium induced:
	  • Amiloride if ongoing Li use
	  • Consider acetazolamide
	  • Malnutrition with poor medullary concentration gradient: consult nutrition
	  • Hypokalemia or hypercalcemia: correct electrolyte abnormalities
	• Other nonspecific therapy: nonsteroidal anti-inflammatory drugs (indomethacin 2 mg/kg/d)

Mineralocorticoid excess	Low dose diuretic
Osmotic diuresis	• Reduce solute load • Control glucose in patients with diabetes mellitus

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DDAVP, desmopressin.

[a]Evidence level for efficacy is low. Consider these agents only if they are also needed for another indication.

CHAPTER 2

Acid-Base and Potassium Disorders

Phuong-Chi T. Pham, Phuong-Mai T. Pham, Cynthia C. Nast, Hai V. Pham, and Phuong-Thu T. Pham

ACID-BASE DISORDERS

Role of Kidneys in Acid-Base Regulation

Proximal tubules: bicarbonate reabsorption (Figure 2.1)

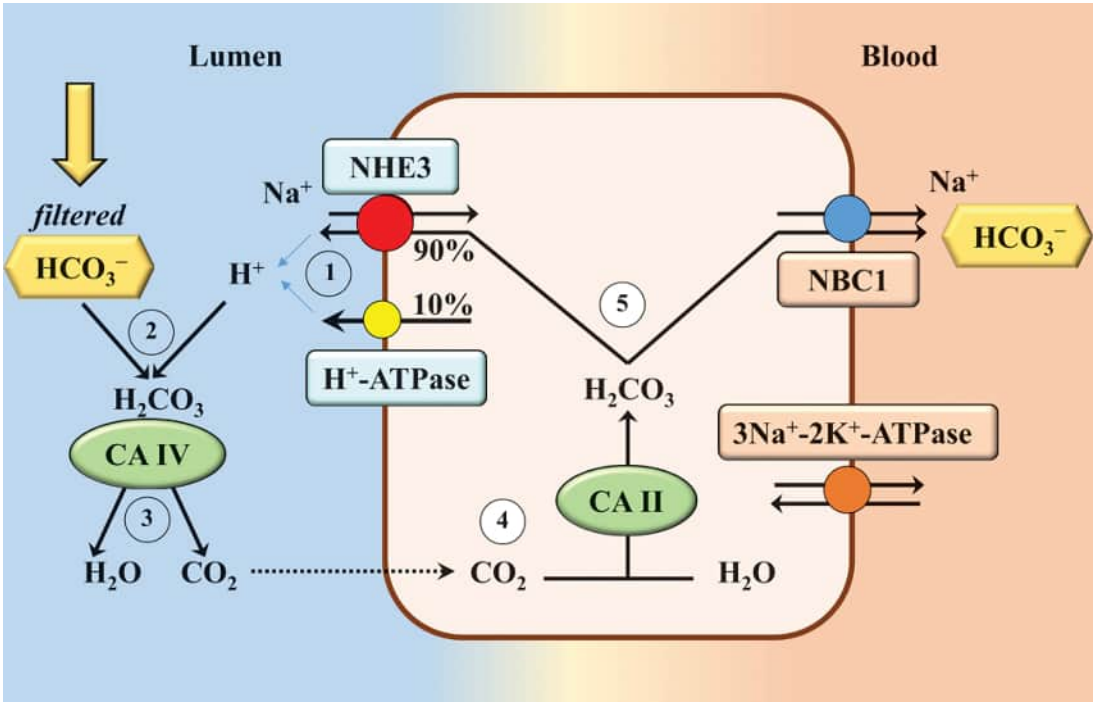


FIGURE 2.1 Bicarbonate reabsorption in proximal tubules. Eighty percent to 85% of HCO_3^- is reabsorbed in proximal tubules. 1. The Na^+-H^+ antiporter NHE3, and to a lesser extent, H^+-ATPase secrete H^+ into the lumen. 2. Secreted H^+ binds filtered HCO_3^- to form carbonic acid (H_2CO_3). 3. CA IV catalyzes the dissociation of H_2CO_3 into H_2O + CO_2. 4. CO_2 diffuses into the cell, combines with H_2O to reform H_2CO_3 (via the catalytic activity of CA II), then again redissociates to H^+ + HCO_3^-. 5. H^+ is resecreted into the lumen, while HCO_3^- is reabsorbed via the Na^+-HCO_3^- exchanger NBC1.

Abbreviations: AQP1, aquaporin 1; CA II, carbonic anhydrase II; CA IV, carbonic anhydrase IV; NBC1, sodium bicarbonate cotransporter-1; NHE3, sodium-hydrogen exchanger-3.

- 80%-85% of filtered HCO_3^- is reabsorbed in the proximal tubules; 15%-20% is reabsorbed in the thick ascending loop of Henle; approximately 5% is reabsorbed in the distal nephron. Although distal HCO_3^- reabsorption is low, this can increase in proximal renal tubular acidosis (pRTA).
- The Na^+-H^+ antiporter NHE3 (sodium-hydrogen exchanger), and to a lesser extent H^+-ATPase, secrete H^+ into the lumen where it binds filtered HCO_3^- to form carbonic acid (H_2CO_3). Carbonic anhydrase IV (CA IV) catalyzes the dissociation of H_2CO_3 into H_2O + CO_2. CO_2 diffuses into the cell, combines with intracellular H_2O to reconstitute H_2CO_3, which then redissociates into H^+ + HCO_3^-. H^+ is resecreted into the lumen, while HCO_3^- is reabsorbed via the Na^+-HCO_3^- exchanger NBC1 (sodium bicarbonate cotransporter 1).
- In acute metabolic acidosis, cytoplasmic NBC1 is recruited into basolateral membranes to increase HCO_3^- reabsorption.
- In metabolic alkalosis, NBC1 is redistributed into the cytoplasm to reduce HCO_3^- reabsorption.
- In respiratory acidosis, NBC1 protein synthesis is upregulated.
- In volume depletion or renal hypoperfusion, angiotensin II (Ang II) stimulates NHE3 and NBC.

Distal tubules: hydrogen secretion and reabsorption (Figure 2.2)

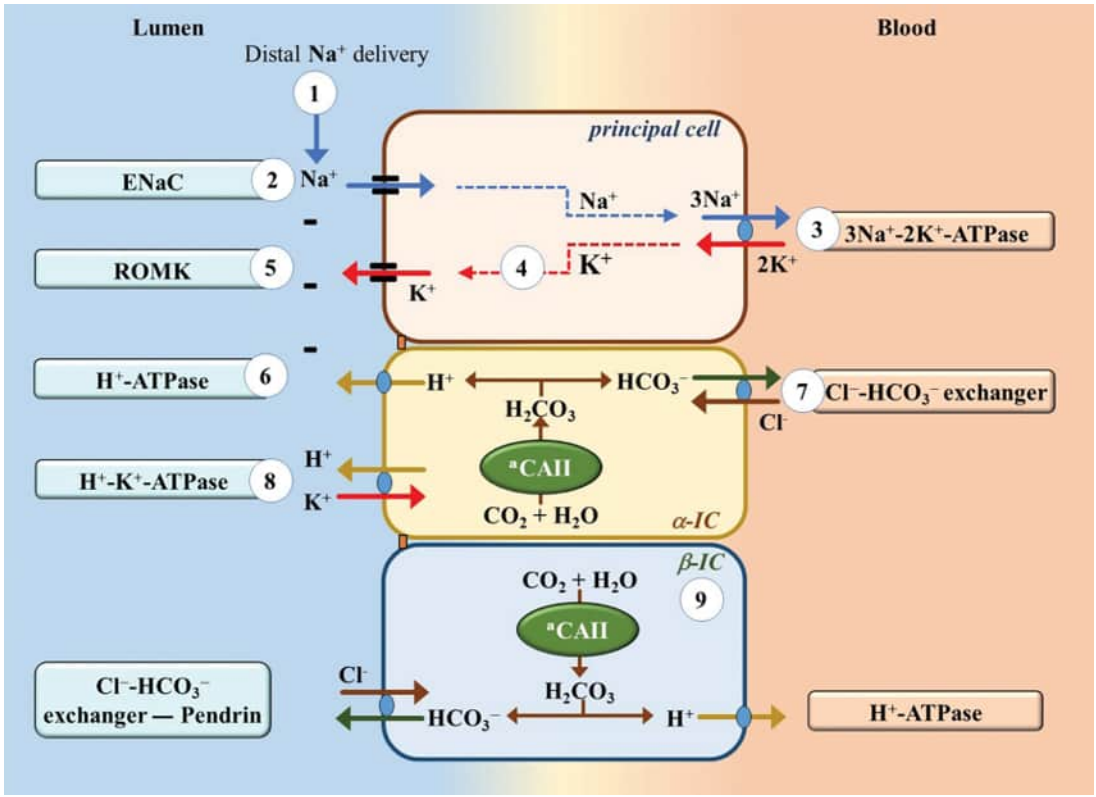


FIGURE 2.2 **H^+, HCO_3^-, and K^+ handling in collecting duct.** 1. Sodium delivery to connecting segment/collecting duct. 2. Na^+ enters principal cells via apical ENaCs. 3. The reabsorbed Na^+ is subsequently reabsorbed on the basolateral side in exchange for cellular K^+ uptake via $3Na^+$-$2K^+$-ATPase. 4. The increased intracellular K^+ gives rise to a favorable chemical gradient for K^+ secretion (ie, intracellular K^+ concentration is greater than that in the tubular lumen). 5. The apical uptake of Na^+ also creates an electronegative lumen that favors the secretion of positively charged K^+ via ROMK in principal cells and 6. Secretion of H^+ via H^+-ATPase in α-intercalated cell. 7. For every H^+ secreted via H^+-ATPase, one equivalent HCO_3^- is reabsorbed via the Cl^--HCO_3^- -exchanger, aka anion exchanger. 8. H^+-K^+-ATPase plays a minor role in acid-base regulation but can be upregulated in hypokalemia and contribute to metabolic alkalosis. 9. β-intercalated cells are mirror images of α-intercalated cells in terms of acid-base regulation. Mutation of pendrin in β-intercalated cells can cause metabolic alkalosis.
Abbreviations: α-IC, α-intercalated cell; β-IC, β-intercalated cell; CA II, carbonic anhydrase II; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel.
[a]CAII, Carbonic anhydrase II combines CO_2 and H_2O to form carbonic acid H_2CO_3. Carbonic acid then dissociates into the proton H^+ and HCO_3^-.

H^+ secretion

Proton (H^+) secretion occurs predominantly in the late distal tubule, connecting segment (CN), cortical and medullary collecting tubules, collectively known as the aldosterone sensitive distal nephron (ASDN) segment, at approximately 1 mmol/kg/d, reflecting daily dietary acid load.

Mechanisms of H^+ and K^+ secretions

- Sodium enters principal cells via apical amiloride-sensitive epithelial sodium channels (ENaCs).
- The reabsorbed Na^+ is subsequently reabsorbed on the basolateral side in exchange for cellular K^+ uptake via $3Na^+$-$2K^+$-ATPase. The increase in cellular K^+ creates a favorable chemical gradient for K^+ secretion.
- The apical uptake of Na^+ via ENaC also creates a relative electronegative lumen that favors the secretion of positively charged K^+ via renal outer medullary potassium channels (ROMK) and H^+ via H^+-ATPase in type A (α-intercalated cells [α-ICs]).
- Aldosterone stimulates both H^+ and K^+ secretion by increasing the expression of ENaC and Na^+-K^+-ATPase and ROMK activity.
- The efficiency of H^+ secretion at ASDN depends in part on the presence of ammonia (NH_3), which serves to buffer the secreted H^+ and facilitate its urinary excretion.

$$H^+ + NH_3 \rightarrow NH_4^+ \text{ (excreted into urine)}$$

NOTE

- Optimal H^+ and K^+ secretions require adequate Na^+ delivery to ASDN, intact ENaC activity, presence of aldosterone, functional mineralocorticoid receptor (MR), and good urine flow.
- The efficiency of H^+ secretion depends in part on the presence of ammonia (NH_3), which serves to buffer the secreted H^+ and facilitate its excretion: $H^+ + NH_3 \rightarrow NH_4^+$.
- Potassium-depleted state enhances the activity of H^+-K^+-ATPase which serves to increase K^+ reabsorption in exchange for H^+ secretion. (This partly explains how K^+ depletion can result in the generation of metabolic alkalosis.)

H^+ reabsorption

- Cortical collecting ducts (CCDs) have type β-intercalated cells (β-ICs) which are thought to be mirror image of α-ICs in terms of H^+/HCO_3^- secretion.
- β-IC secrete HCO_3^- in exchange for the reabsorption of luminal Cl^- via the apical Cl^--HCO_3^- exchanger (aka anion exchanger [AE] or pendrin) and reabsorb H^+ on the basolateral cell surface. In contrast, α-ICs secrete H^+ into the lumen while reabsorbing HCO_3^- on the basolateral side.
- Depending on the acid-base status, distal tubules can switch intercalated cell types to secrete either H^+ or HCO_3^-. Chronic metabolic acidosis increases the proportion of α-IC while metabolic alkalosis increases the proportion of β-IC. Extracellular matrix proteins (eg, hensin, galectin 3, and others) along the intercalated cell's basolateral surface have been suggested to play a role in the expression switch of this cell type (see **Figure 2.2**).

Ammoniagenesis: proximal tubular production of NH_4^+, NH_3 (Figure 2.3)

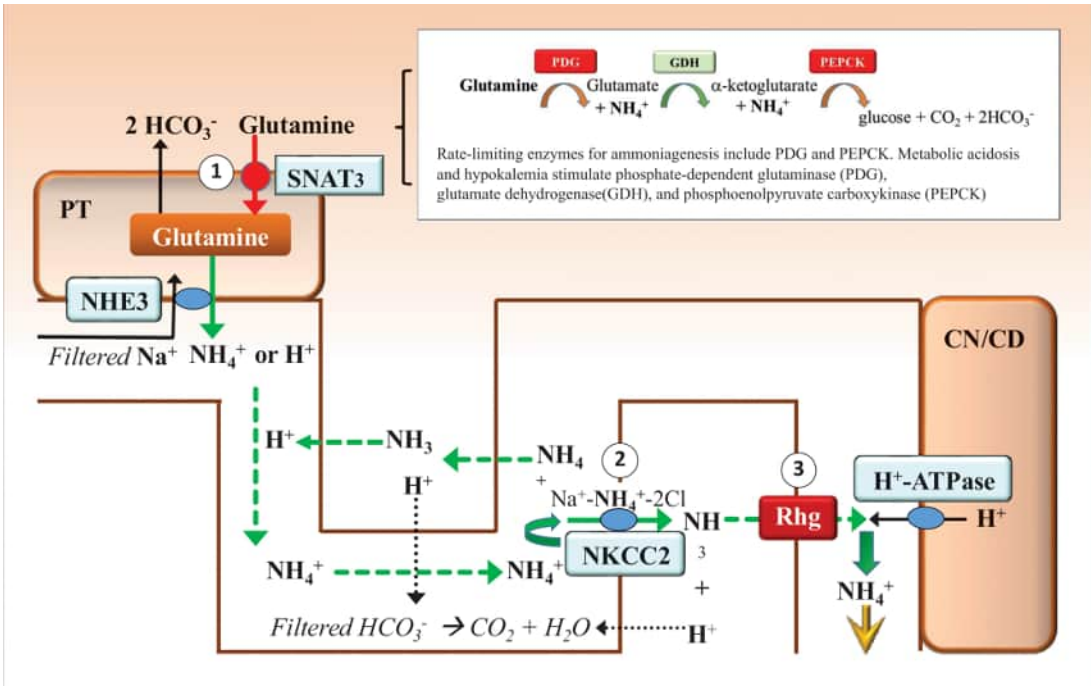


FIGURE 2.3 **Ammoniagenesis.** 1. NH_4^+ generated from glutamine in the proximal tubule are secreted into the lumen via NHE3. 2. Luminal NH_4^+ may be reabsorbed at the loop of Henle via NKCC2. 3. Secretion of NH_3 at aldosterone sensitive segment is facilitated by nonerythroid glycoproteins RhBg and RhCg.
Abbreviations: CN/CD, connecting segment/collecting duct; NHE3, sodium-hydrogen exchanger 3; NKCC2, sodium-potassium 2 chloride cotransporter; PT, proximal tubule; Rhg, nonerythroid glycoproteins B and C (RhBg, RhCg); SNAT3, sodium-dependent amino acid transporter.

- The substrate for ammoniagenesis is glutamine.
- Glutamine is taken up by proximal tubular cells via the sodium-dependent amino acid transporters (SNAT3), where NH_4^+ is formed in a multistep process.
  - Rate-limiting enzymes for ammoniagenesis include phosphate-dependent glutaminase (GA) and phosphoenolpyruvate carboxykinase (PEPCK).
  - NH_4^+ is either transported as NH_4^+ into the lumen via NHE3 or freely diffuses into lumen as NH_3. Ang II upregulates NHE3, thereby increasing NH_4^+ secretion.
  - Luminal NH_3 and NH_4^+ are reabsorbed at thick ascending limb loop of Henle (TAL) into the interstitium, where they are subsequently secreted into CCD with H^+. NH_4^+ may be reabsorbed at TAL via Na^+-K^+-$2Cl^-$-cotransporters (NKCC2). Secretion of NH_3 at CNs and collecting tubules is facilitated by the

nonerythroid glycoproteins RhBg (Rhesus blood group glycoprotein B) and RhCg (Rhesus blood group glycoprotein C).

- Ammoniagenesis and ammonia transport along the nephron are stimulated by metabolic acidosis and hypokalemia.

FYI

- Metabolic acidosis and hypokalemia:
  - Increase ammoniagenesis by increasing the expression of involved enzymes including GA, glutamate dehydrogenase, and PEPCK.
  - Facilitate the transport of ammonia along the nephron by increasing the expressions of SNAT3, NHE3, and Rh glycoprotein RhCg.
- Metabolic acidosis also:
  - Increases mobilization of glutamine from skeletal muscle and intestinal cells
  - Increases the expression of NKCC2

Diagnosis of Acid-Base Disorders

- In the evaluation of acid-base disorders, the use of either arterial or venous blood gas (ABG and VBG, respectively) generally provides similar answers.
- Nonetheless, on average, the differences in ABG vs VBG for pH, P_{CO_2}, and HCO_3^- are as follows:
  - pH (ABG) ≈ pH (VBG) + 0.03
  - P_{CO_2} (ABG) ≈ P_{CO_2} (VBG) − 4
  - HCO_3^-(ABG) ≈ tCO_2 (VBG) − 1
  - Venous tCO_2 is higher than [HCO_3^-] from an ABG because venous tCO_2 measures HCO_3^-, H_2CO_3, and dissolved CO_2 gas. Venous tCO_2 ≈HCO_3^- + H_2CO_3 + dissolved CO_2 ≈ HCO_3^- + (P_{CO_2} × 0.03) and is typically 1 to 1.5 mmol/L higher than [HCO_3^-].

NOTE

In circulatory failure where alveolar gas exchange is intact but blood delivery to the lungs for gas exchange is severely reduced, an ABG may reveal normal oxygenation and normal to low P_{CO_2} while VBG might show severe hypoxia and hypercapnia. Differences in pH, P_{CO_2}, and HCO_3^- would thus widen, in which case ABG and VBG may not be used interchangeably to accurately predict acid-base disorders.

Study **Supplement S2.1** on acid-base disorder determination and practice problems.

METABOLIC ACIDOSIS, ELEVATED SERUM ANION GAP (SAG)

Study **Supplement S2.2** for clinical significance of SAG and conditions associated with abnormal SAG (both low and high SAG conditions).

- When SAG, an estimate of serum (unmeasured **Anions**$^-$ – unmeasured Cations$^+$), is calculated as serum [Na^+] – [Cl^-] – [HCO_3^-], the normal range is 12 ± 2 mmol/L. The normal range of SAG may vary slightly among different laboratories.
- A SAG is typically considered high when it is greater than 12 ± 2 mmol/L.

Conditions With High SAG Metabolic Acidosis

- Acids may be denoted as HA = H^+ + **Anion**$^-$. The presence of an acid can be deduced from the presence of its anion$^-$, evidenced as a rise in SAG (↑unmeasured **Anions**$^-$ – unmeasured Cations$^+$). Conditions associated with elevated SAG metabolic acidosis include the following:
  - Methanol (converted to formic acid; formic acid in turn inhibits mitochondrial function and leads to lactic acid [LA] accumulation)
  - Metformin (inhibits mitochondrial function and leads to LA accumulation)
  - *Uremia (accumulation of sulfates, phosphates, urates, etc, occurs at an estimated glomerular filtration rate [eGFR] of <15 mL/min/1.73 m^2)
  - Diabetic ketoacidosis (DKA; acetoacetate [AcAc], β-hydroxybutyrate [β-OH])
  - Paraldehyde (causes hypotension and subsequent LA accumulation)
  - *Pyroglutamate (aka 5-oxoproline [OXO]) with chronic acetaminophen use
  - *Propylene glycol (PG) (metabolizes to lactate)
  - Isoniazid (inhibits lactate dehydrogenase and leads to LA accumulation)
  - Iron overload (inhibits mitochondrial function and leads to LA accumulation)
  - *L-Lactic acidosis
  - *Ethylene glycol (glycolate, oxalate)
  - *Salicylic acid (salicylate)
  - *Short bowel syndrome with D-LA produced from bacterial overgrowth (may present as normal or elevated SAG depending on kidney function, ability to filter and excrete D-lactate)

*Special conditions with high SAG metabolic acidosis are discussed below.

Pyroglutamate aka 5-Oxoproline With Chronic Acetaminophen Use

- Chronic acetaminophen use in malnourished or chronically ill patients may be associated with elevated SAG metabolic acidosis due to the excess production of OXO (aka pyroglutamic acid [PA]) by γ-glutamylcysteine synthetase from the γ-glutamyl cycle. This is due to the lack of negative feedback of γ-glutamylcysteine synthetase activity by glutathione. In physiologically stressed or malnourished patients with increased oxidative stress, glutathione levels are reduced. The additional use of acetaminophen further depletes glutathione because glutathione is used in the metabolism of acetaminophen.
- Suspect this condition in patients with chronic acetaminophen use who present with elevated SAG metabolic acidosis in the absence of lactate or ketones.
- Other notable findings:
  - Acetaminophen level may be low or negative because this is associated with long-term use of acetaminophen, not acute overdose. In acute acetaminophen poisoning, patients present with high acetaminophen levels and possibly lactic acidosis, the latter in the setting of acute fulminant liver failure
  - Elevated serum osmolality gap (SOG) due to accumulation of OXO/PA
- Management: fluid support, consider acetylcysteine therapy to replete glutathione.

Propylene Glycols

- PG is used as a solvent in several medications (eg, topical sulfadiazine silver cream, intravenous nitroglycerin, multivitamins, phenobarbital, phenytoin, lorazepam, or diazepam used in acute alcohol withdrawals, etomidate, enoximone)—Note: Midazolam does not contain PG.
- PG is metabolized to L-lactate, resulting in elevated SAG metabolic acidosis.
- In the setting of ongoing use of PG-containing medications, suspect PG-induced lactic acidosis in culture-negative, sepsis-like cases with increased LA levels.
- Other notable signs and symptoms associated with PG accumulation: increased serum osmolality, hemolysis, arrhythmias, hypotension, multiorgan failure, seizures, coma
- Management: supportive therapy, offending drug withdrawal, hemodialysis in severe cases with multisystem organ failure

Lactic Acidosis

- An average adult generates 1,500 mmol of LA daily from the brain (25%), muscle (25%), skin (25%), red blood cells (RBC; 20%), and intestines (10%).
- Physiologic roles of LA: precursor for renal gluconeogenesis, source of energy for cardiomyocytes, immune cells, immunomodulation, angiogenesis, wound healing
- Altered metabolism of LA can lead to a high SAG metabolic acidosis, aka lactic acidosis, that can be classified as type A and type B based on underlying etiology (**Figure 2.4**).

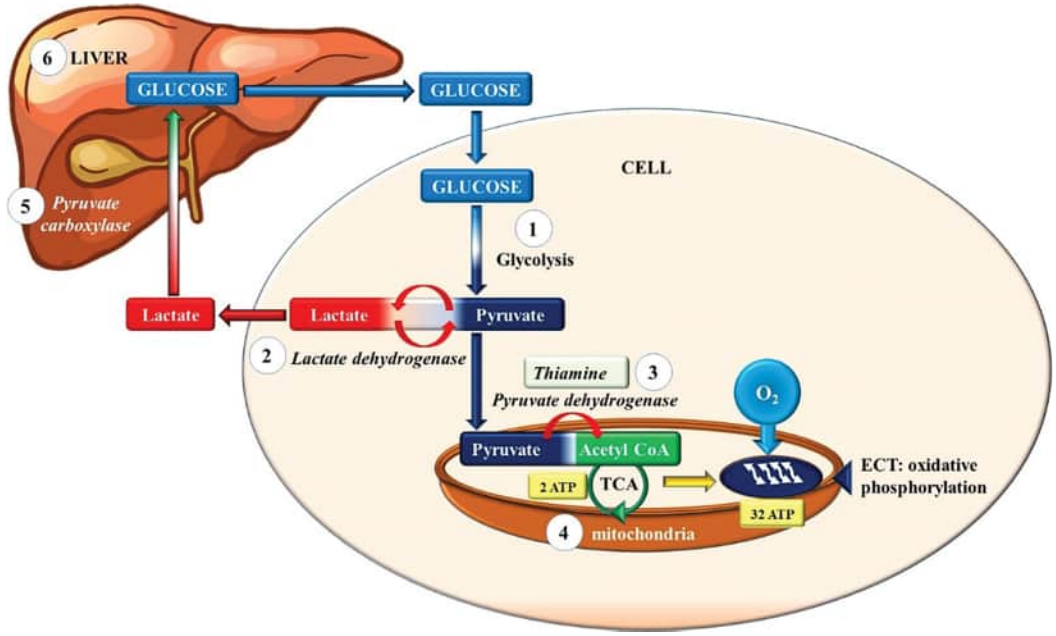


FIGURE 2.4 Lactic Acidosis.

Glucose is taken up by the cell where it undergoes glycolysis to form pyruvate. Pyruvate either forms lactate via lactate dehydrogenase or enters the mitochondria where it is metabolized to acetyl-CoA via pyruvate dehydrogenase. Thiamine is a cofactor for pyruvate dehydrogenase. In the mitochondria, acetyl-CoA enters the tricarboxylic acid cycle (TCA), where two ATPs are produced. NADH and $FADH_2$ formed from TCA are shuttled to the electron transport chain for oxidative phosphorylation, a process whereby 32 more ATPs are produced in the presence of oxygen.

Type A lactic acidosis occurs under hypoxic conditions where oxidative phosphorylation is compromised by the lack of oxygen. This leads to anaerobic metabolism, accumulation of pyruvate, and subsequent conversion to lactate.

Type B lactic acidosis occurs via defects/problems at any other steps unrelated to the lack of oxygen.

1. Excessive glycolysis: caffeine intoxication with overactive sympathetic nerve activity, high-dose β2-agonist used in the treatment of asthma, pheochromocytoma, metabolically active malignant cells
2. Lactate dehydrogenase inhibition in the conversion of lactate to pyruvate: isoniazid
3. Inadequate thiamine: metabolically active malignant cells or alcoholism in combination with severe malnutrition
4. Drugs/toxins that cause mitochondrial injury and/or oxidative phosphorylation: methanol, propofol, linezolid, sodium thiosulfate, salicylate, cyanide, mangostin, nucleosides (eg,

didanosine, lamivudine, stavudine), reverse transcriptase inhibitors (eg, abacavir, tenofovir), valproate

5. Inhibition of pyruvate carboxylase: Metformin is thought to cause lactic acidosis by inhibiting oxidative phosphorylation and pyruvate carboxylase.
6. Liver failure can limit gluconeogenesis and cause the accumulation of LA.

Abbreviations: ATP, adenosine triphosphates; ECT, electron chain transport; TCA, tricarboxylic acid cycle.

- LA can be buffered intracellularly and in bones, thereby reducing consumption of bicarbonate. Unlike other elevated anion gap (AG) metabolic acidosis, where every 1 mmol H^+ is buffered by 1 mmol HCO_3^-, every 1.6 mmol LA only requires 1 mmol of HCO_3^- for buffering (instead of 1.6 mmol HCO_3^-).
- Treatment of lactic acidosis:
  - Treat underlying causes and improve tissue perfusion.
  - Survival benefit with HCO_3^- infusion has not been shown.
  - Bicarbonate infusion may be considered in patients with severe metabolic acidosis.

NOTE

Caution with the use of bicarbonate drip because it can:

- Lower ionized calcium level
- Exacerbate hypokalemia
- Worsen CO_2 retention and potential development of CO_2 narcosis in patients with baseline respiratory acidosis
- Cause volume overload in patients with poor kidney function

Type A L-lactic acidosis (L-isoform lactic acidosis)

- Mechanism: increased circulating epinephrine levels associated with high-stress states and hypoxemia lead to increased anaerobic glycolysis, hence downstream LA formation.
- Conditions with type A lactic acidosis: sepsis, severe prolonged hypotension, cardiogenic shock, vigorous exercise, seizures, tissue hypoperfusion, hypoxia (including severe anemia), carbon monoxide poisoning

Type B L-lactic acidosis (L-isoform lactic acidosis)

- Multiple mechanisms are possible, but none is related to tissue hypoperfusion or hypoxia.
- Conditions associated with type B, L-lactic acidosis may arise from increased metabolism, mitochondrial dysfunction, liver dysfunction, or any enzymes associated with lactate metabolism.

Increased glycogenolysis, glycolysis, lipolysis

- Malignancies: leukemias, lymphoproliferative malignancies, tumors involving liver metastatic disease; may be ameliorated with thiamine
- Toxic levels of caffeine, β2-agonists or β2 stimulation (eg, treatment of asthma, pheochromocytoma). Treatment: β-blocker

> **NOTE**
>
> In the patient with asthma, lactic acidosis may arise from the use of β2-agonist (type B) or from tissue hypoxia due to respiratory distress (type A). Differentiation between the two types of lactic acidosis depends on patient's respiratory status and overall well-being. Lactic acidosis from β2-agonist is benign, but lactic acidosis from respiratory failure is ominous.

- Diabetic ketoacidosis

Inherited mitochondrial disease leading to defective oxidative phosphorylation

Acquired mitochondrial dysfunction leading to defective oxidative phosphorylation

- Metformin
  - Mechanisms: Inhibits pyruvate carboxylase and complex 1 in the mitochondrial respiratory chain
  - Risks for metformin-induced LA: reduced kidney function (eGFR <30 mL/min/1.73 m^2), hypotension, advanced age, concurrent use of nephrotoxins (eg, intravenous radiocontrast agent), liver dysfunction
  - Kidney replacement therapy is indicated in severe cases where lactate level exceeds 20 mmol/L, pH 7.0 or less, presence of shock, altered mental status, liver dysfunction, kidney failure
- Sodium thiosulfates (STS) used in the treatment of calcific uremic arteriolopathy (calciphylaxis) may be associated with an elevated SAG metabolic acidosis due to lactic acidosis (STS interference with mitochondrial oxidative phosphorylation) and the formation of thiosulfuric acid and hydrogen sulfide from STS.
- Other drugs that can interfere with oxidative phosphorylation: propofol, linezolid, nucleosides (lamivudine, zidovudine, stavudine, didanosine), reverse transcriptase inhibitors (abacavir, tenofovir), valproate (mitochondrial dysfunction and hepatotoxicity), toxic alcohols (methanol [formic acid can inhibit mitochondrial function and increased anaerobic metabolism], salicylates [causes uncoupling of oxidative phosphorylation in mitochondria]), cyanide (mitochondrial toxin), isoniazid, mangosteen (α-mangostin in this Southeast Asian fruit is a potent inhibitor of mitochondria function)

Impaired/insufficient pyruvate dehydrogenase (PDH) activity: active malignant tumors overwhelming enzymatic activity

Severe thiamine deficiency (cofactor of PDH): active malignant tumors or alcoholism with malnutrition
Acute fulminant liver failure leading to impaired lactate clearance

Type B, D-LA (D-LA level >3 mmol/L)

Short bowel syndrome

- In patients with large bowel resections, the D-isomer of LA, D-LA, can be produced from a high-carbohydrate diet by gut bacterial overgrowth and cause D-lactic acidosis. This is NOT the same as what humans predominantly produce, which is the L-lactate isoform.
- Clinical manifestations:
  - Patients with D-lactate typically present with encephalopathy, slurred speech, ataxia, gait disturbances, mimicking a "drunk."
  - D-Lactic acidosis can be exacerbated following high-carbohydrate ingestion and metabolic acidosis.
- Laboratory findings: An elevated SAG metabolic acidosis may be seen at early presentation followed later by normal SAG metabolic acidosis. Renal reabsorption of D-LA is much lower than that of L-LA. The high renal excretion of D-lactate can lead to a normal SAG in well-hydrated individuals with good kidney function.
- Treatment: oral metronidazole or vancomycin, supportive

Diabetic ketoacidosis

D-Lactate is derived from methylglyoxal, a metabolite of acetone and dihydroxyacetone phosphate, which are intermediates that can accumulate in DKA. D-Lactate may be elevated in severe DKA.

Propylene glycol intoxication with D-lactic acidosis (case report)

Ketoacidosis

Ketoacidosis (eg, alcoholic, starvation, and DKA) occurs when hepatic lipid metabolism is switched to a state of glucagon-driven ketogenesis due to relative or absolute insulin deficiency.

Alcohols (Ethanol, Methanol, Glycols)

- Ingestion or infusion of any alcohol will increase the serum osmolality because the alcohol molecules will contribute to the total serum osmolality. The measured serum osmolality will, therefore, exceed that expected from the usual components within the serum. Whenever there is a suspicion for intoxication/poisoning, calculate the SOG.

- SOG
  - SOG = (Measured S_{OSM} – calculated S_{OSM})
  - Where calculated S_{OSM} = ($S[Na^+]$ + $S[K^+]$) × 2 + blood urea nitrogen (mg/dL)/2.8 + glucose (mg/dL)/18 + LA (mmol/L) + ethanol (mg/dL) × 4.6. LA and ethanol are included in calculated S_{OSM} because the goal of checking SOG is to uncover solutes other than these molecules.
  - An SOG much greater than 12 mOsm/L indicates the presence of solutes other than those accounted for in the preceding equation and prompts an immediate evaluation for ingestion of toxic solutes (ie, methanol, ethylene glycol, isopropanol, or toluene, ketones, pyruvate, etc).

See **Figure 2.5** and **Table 2.1** for clinical manifestations, metabolism, and management of alcohol intoxications including ethanol, methanol, PG, and ethylene glycol.

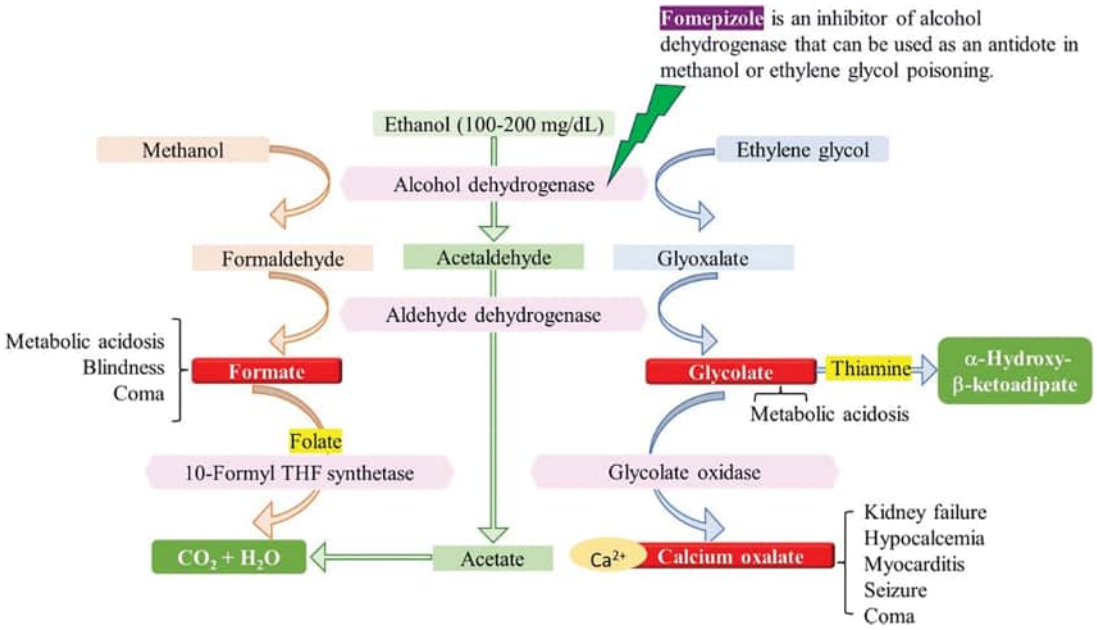


FIGURE 2.5 **Metabolism of methanol and ethylene glycol.** Both methanol and glycol alcohols undergo metabolism to their respective toxic metabolites via alcohol dehydrogenase. Ethanol is also a substrate for alcohol dehydrogenase and may be used as a competitive antagonist to reduce the metabolism of methanol and glycol alcohols. Ethanol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to form acetate, which is subsequently metabolized to CO_2 and H_2O. Optimal efficacy of ethanol as a competitive inhibitor of alcohol dehydrogenase occurs at levels ranging between 100 and 200 mg/dL. Fomepizole is an inhibitor of alcohol dehydrogenase that can also be used as an antidote in methanol or ethylene glycol poisoning.
Abbreviation: THF, tetrahydrofolate.

Table 2.1 Alcohol intoxication

Alcohols[a]	Ethanol	Methanol	Ethylene glycol (antifreeze)	[b]Propylene glycol (used as solvent for many drug formulations)	Isopropyl alcohol (rubbing alcohol)
Associated anion	β-Hydroxybutyrate	Formate	Oxalate, glycolate	L-Lactate	None
Clinical complications and comments	• Severe metabolic acidosis with rapid response to IVF • Risks for ethanol (alcohol) ketosis: poor carbohydrate intake, volume depletion, insulin deficiency	Blindness	Kidney failure, calcium oxalate precipitation	Sepsis-like presentation (eg, hypotension, high lactate levels, high AG metabolic acidosis), hemolysis, arrhythmias, multiorgan failure, seizures, coma	• Central nervous system suppression, nausea, vomiting • Usually not fatal with proper supportive care
Treatment	IVF support (eg, dextrose PLUS normal saline), thiamine, and nutritional support	• Fomepizole • Folinic acid 50 mg IV q6h to increase metabolism of formic acid to CO_2 + H_2O	• Add fomepizole if ethylene glycol level >20 mg/dL and S_{OSM} >20 mOsm/kg. Continue until <20 (or <10 mg/dL in the presence of end-organ damage). • Alkalinize to achieve pH >7.35 • IV thiamine 100 mg + pyridoxine 50 mg to increase metabolism	• Discontinue offending agent. • Supportive, airway protection	Supportive, airway protection

Alcohols[a]	Ethanol	Methanol	Ethylene glycol (antifreeze)	[b]Propylene glycol (used as solvent for many drug formulations)	Isopropyl alcohol (rubbing alcohol)
			of glyoxylate		
Dialysis indications	Multiorgan failure or severe metabolic acidosis not responding to fluid administration	• Level >50 mg/dL (methanol or ethylene glycol) in association with severe metabolic acidosis or end-organ damage (use large dialyzer, blood flow >300 mL/min). • NOTE: 1. fomepizole and ethanol are dialyzable. Dose adjustments are needed. 2. Must monitor potassium, phosphorus, and magnesium and replace as needed.		Multiorgan failure, severe hemodynamic instability	Refractory and severe hemodynamic instability in association with blood levels >500 mg/dL and [c]serum osmolar gap >100 mOsm/kg

Abbreviations: AG, anion gap; IV, intravenous; IVF, intravenous fluid.

[a]Methanol, ethylene glycol, and propylene glycol intoxication can give rise to an elevated serum anion gap metabolic acidosis. Isopropyl alcohol does not cause metabolic acidosis or an increase in serum anion gap. Isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, which is a ketone but NOT an acid or an anion. Serum and urine "ketones" may be positive, but there is NO metabolic acidosis or any increase in serum anion gap.

[b]Examples of propylene glycol-containing drugs: topical sulfadiazine silver cream, IV nitroglycerin, multivitamins, phenobarbital, phenytoin, lorazepam, diazepam, etomidate, enoximone—Note midazolam does not contain propylene glycol.

[c]High blood levels of any alcohol ingested can present with high serum osmolar gap.

Alcohol ketoacidosis (AKA)

Individuals with a history of alcoholism, typically with a recent history of binge drinking and concurrent poor oral intake, persistent vomiting, and/or volume depletion, are at risk for AKA.

Clinical manifestations

- Sweet ketone breath
- Elevated SAG metabolic acidosis may be severe with plasma pH less than 7.
- Mixed acid-base disorders may be present including metabolic alkalosis from vomiting and volume depletion.

Mechanisms of ketoacidosis in AKA

- Poor oral intake → ↓insulin and ↑glucagon, leads to:
  - Increased lipolysis and free fatty acid (FFA) release from peripheral adipose tissues (lipase is normally inhibited by insulin)

    - Increased transport of FFA into mitochondria where FFA undergoes oxidation and ketone body formation
    - ↓Insulin reduces ketone body utilization by insulin-sensitive tissues.
- Elevated ratio of the reduced nicotinamide adenine dinucleotide NADH to NAD^+ due to the metabolism of alcohol leads to:
    - Impaired conversion of lactate to pyruvate which then leads to increased lactate levels
    - Impaired gluconeogenesis
    - A shift in β-OH to AcAc equilibrium toward β-OH. Unlike DKA where ketone bodies include acetone, AcAc, and β-OH, the predominant ketone body in AKA is β-OH.
    - Volume depletion → ↓renal perfusion, reduced urinary excretion of ketoacids

Treatment

- Glucose + normal saline (dextrose increases insulin, stimulates oxidation of NADH to NAD^+) infusion can rapidly correct the metabolic acidosis.
- Thiamine to reduce the risk of precipitating Wernicke encephalopathy or Korsakoff syndrome associated with glucose administration
- Electrolytes monitoring and replacement (particularly those associated with the refeeding syndrome, eg, phosphorus, magnesium, potassium)
- Hemodialysis may be considered in severe metabolic acidosis with poor response to conservative supportive therapy outlined earlier.

Starvation ketoacidosis (SKA)

- Occurs when hepatic glycogen stores are depleted and lipolysis is stimulated
- SKA usually presents with mildly elevated SAG because ketoanion levels are typically only 3 to 5 mmol/L. The ketone bodies initially produced in SKA can in turn stimulate pancreatic islets to release sufficient insulin to hinder further lipolysis, rendering SKA a self-limiting process.

Diabetic ketoacidosis

The lack of insulin leads to increased mobilization of FFA from adipose tissue to the liver and hepatic lipid metabolism switches to ketogenesis.

Management of DKA

- Insulin administration is key.
- Volume repletion: Normal saline is currently the fluid of choice in the management of DKA. However, a 2022 systematic review and meta-analysis comparing normal saline and balanced-electrolyte solutions (BES, eg, lactated

ringer solution) revealed earlier resolution of DKA with BES. The time to achieving euglycemia, however, may be longer for balanced crystalloids, possibly due to the metabolism of lactate to glucose.

NOTE

- Excess hydration with normal saline and resultant high urine flow can lead to rapid urinary loss of ketone bodies, thereby converting a high SAG metabolic acidosis to a normal SAG metabolic acidosis, aka hyperchloremic metabolic acidosis. Ketone bodies are the source of rapid bicarbonate generation with insulin administration. Urinary loss of ketone bodies may thus prolong the acidemic state.
- The treatment of DKA in patients with anuria who need dialysis typically only requires insulin administration with or without gentle fluid resuscitation to match poor oral intake and/or associated fluid loss (eg, vomiting). The purpose of normal saline infusion in DKA is to primarily replace volume loss from osmotic diuresis and/or fluid loss from vomiting, not to "correct" the DKA. It is insulin administration that corrects DKA.

- Severe hypokalemia and hypophosphatemia may follow insulin administration and fluid resuscitation. In cases with significant electrolyte deficiencies, repletion of these electrolytes must be done prior to insulin administration. Note that hypophosphatemia can interfere with renal adenosine triphosphate (ATP)-dependent acid-base regulation and may prolong metabolic acidosis.

NOTE

Serum ketones may also be present with isopropyl alcohol intoxication (aka isopropanol, rubbing alcohol). Isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone which evaporates with breathing (fruity breath odor). Acetone is not an acid or an anion. Thus, isopropyl alcohol intoxication does cause metabolic acidosis or elevated SAG.

Ketoacidosis with sodium-glucose transporter-2 inhibitors (SGLT2i)

Greater than 70% of reported cases occurred with serum glucose less than 250 mg/dL. For this reason, SGLT2i-associated ketoacidosis is also referred to as "euglycemic ketoacidosis."

Mechanism: This is thought to be due to an imbalance in insulin and glucagon ratio. SGLT2i glucose-lowering effect reduces insulin secretion, thereby allowing unopposed glucagon to induce lipolysis and ketoacidosis.

Clinical manifestations: nonspecific symptoms such as abdominal pain, nausea/vomiting, and/or fatigue and evidence of an increased SAG. Volume depletion is typically mild or absent due to the lack of severe hyperglycemia and associated osmotic diuresis.

Risks: diabetes mellitus (DM) type 1, female, excessive reduction or discontinuation of insulin, major surgery or trauma, reduced oral intake, alcohol consumption, concurrent use of metformin, low-carbohydrate intake (eg, ketogenic diets)

Risk reduction of SGLT2i-associated ketoacidosis

- The use of SGLT2i in patients with DM type 1 is contraindicated (FDA [U.S. Food and Drug Administration] warning).
- Discontinue SGLT2i in acute illnesses, particularly in association with poor oral intake.
- Discontinue SGLT2i 48 to 72 hours prior to major surgery.
- Avoid insulin dose reduction of greater than 20%.
- Avoid ketogenic diets and alcohol ingestion.
- Permanently discontinue SGLT2i in patients with SGLT2i-associated ketoacidosis.
- Treatment is similar to DKA. However, patients with SGLT2i-associated ketoacidosis may need early glucose infusion (ie, 5% or 10% dextrose drip) to prevent hypoglycemia while concurrently allowing for sufficient endogenous insulin secretion to suppress ketone formation and close the SAG.

Ketoacidosis while receiving continuous kidney replacement therapy (CKRT)

- Ketoacidosis has been reported in critically ill patients with diabetes (with or without prior insulin need) with poor oral intake while receiving CKRT with glucose-free solutions.
- Suspect ketoacidosis in critically ill patients with diabetes receiving adequate CKRT but having persistent high AG metabolic acidosis that is not explained by lactic acidosis.

Mechanisms: CKRT-associated ketoacidosis is thought to result from a reduced insulin-to-glucagon ratio. Reduced endogenous insulin secretion is thought to be associated with poor caloric intake and glucose loss with the use of glucose-free CKRT solutions.
Laboratory findings: metabolic acidosis with elevated SAG, elevated β-OH level
Treatment: glucose supplement + insulin

Salicylate intoxication

Salicylates are widely available over the counter as a primary drug or compounded into formulations with narcotics, antihistamines, or anticholinergic agents.
Acid-base disturbances associated with salicylates:

- Direct stimulation of the cerebral medulla causes hyperventilation, respiratory alkalosis.

- As salicylates are metabolized, they cause uncoupling of oxidative phosphorylation in the mitochondria, leading to anaerobic metabolism which in turn results in lactic acidosis.
- Further hyperventilation to compensate for the lactic acidosis can lead to respiratory fatigue and eventual respiratory acidosis if medical intervention does not occur.

Management

- Consult toxicology.
- Airway protection, mechanical ventilation as needed
- Fluid resuscitation with 5% dextrose and 150 mmol/L sodium bicarbonate solution. Dextrose prevents any potential central nervous system hypoglycemia. Alkalinization corrects metabolic acidosis and reduces brain uptake of salicylates.
- Correct other electrolytes as needed, in particular, hypokalemia.
- Hemodialysis indications: severe acidosis or hypotension despite fluid resuscitation, salicylate levels greater than 100 mg/dL, mechanical ventilation, and/or end-organ injury (eg, seizures, rhabdomyolysis, kidney failure, pulmonary or cerebral edema)

Uremia

- High SAG metabolic acidosis typically occurs with eGFR less than 15 mL/min/1.73 m^2.
- The increased SAG is due to the accumulation of urates, sulfates, phosphates, etc.
- In mild to moderate kidney injury, that is, eGFR greater than 15 mL/min/1.73 m^2, metabolic acidosis generally has normal SAG due to adequate renal excretion of organic anions.

METABOLIC ACIDOSIS, NORMAL SAG

- Normal AG metabolic acidosis is traditionally categorized as renal versus extrarenal causes, where the former refers to renal tubular acidosis (RTA).
- The measurement of urine ammonium NH_4^+ levels, urine anion gap (U_{AG}), or urine osmolality gap (UOG) can help differentiate between renal versus extrarenal causes of normal SAG metabolic acidosis.

24-hour urine ammonium

- A high urine NH_4^+ level indicates:
  - Proximal tubules can generate ammonia, NH_3.

- H^+ is secreted by distal segments: $NH_3 + H^+ = NH_4^+$

> **FYI**
>
> NH_3 buffers H^+ secreted by distal tubules to form ammonium, NH_4^+, to increase urine pH. Lone H^+ without NH_3 would result in a lower, more acidic urine pH.

- Reference range for 24 hours urine ammonium is 15 to 56 mmol (Mayo Medical Laboratories).
- Concurrent low urine NH_4^+ and high urine pH suggests low luminal H^+ levels. This is consistent with distal renal tubular acidosis (dRTA).
- In conditions with reduced ammoniagenesis (eg, hyperkalemia inhibition of ammoniagenesis), urine pH may be low because any H^+ secreted is not buffered.
- Concurrent high urine ammonium (NH_4^+) and low urine pH suggest high luminal H^+ levels. This is consistent with increased tubular H^+ secretion for ongoing diarrheal fluid losses. Patients with these findings are susceptible to uric acid and calcium oxalate stones.

Urine anion gap

If 24-hour urine NH_4^+ cannot be measured, U_{AG} may be used to estimate NH_4^+ level.

Conceptualization of U_{AG}

Major cations in the urine including measured Na^+, K^+, unmeasured NH_4^+, and other unmeasured cations are equal to major anions in the urine including measured Cl^-, unmeasured HCO_3^-, and other unmeasured anions.

$$Na^+ + K^+ + NH_4^+ + \text{unmeasured cations} = Cl^- + HCO_3^- + \text{unmeasured anions}$$

Rearranging the equation,

$$Na^+ + K^+ - Cl^- = HCO_3^- - NH_4^+ + \text{unmeasured (anions} - \text{cations)}$$

Ignoring unmeasured (anions − cations) term, the equation is simplified as:

$$Na^+ + K^+ - Cl^- = \mathbf{HCO}_3 - - NH_4^+$$

Interpretation of U_{AG}

- In **extrarenal metabolic acidosis** (eg, diarrhea or exogenous acid load), the kidneys will attempt to correct the metabolic acidosis by increasing HCO_3^- reabsorption while increasing NH_4^+ excretion. This would result in a negative U_{AG}.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = \downarrow \textbf{HCO}_3^- - \uparrow NH_4^+ < 0$$

- In **proximal RTA (pRTA)**, HCO_3^- wasting far exceeds maximal NH_4^+ excretion, hence positive U_{AG}.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = \uparrow HCO_3^- - NH_4^+ > 0$$

- In **distal RTA (dRTA)**, excretion of both HCO_3^- and NH_4^+ is reduced. U_{AG} may remain close to that seen with normal acid-base status, which is typically positive.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = \downarrow HCO_3^- - \downarrow NH_4^+ \approx \text{positive}$$

NOTE

Prior to using U_{AG} to determine renal versus extrarenal causes of metabolic acidosis, it is important to rule out conditions that can affect U_{AG} independent of acid-base disorders. These conditions include urinary excretion of anions such as ketoanions and hippurate/benzoate (metabolites from toluene) and the presence of urea-splitting organisms (elevated NH_4^+ levels produced by bacteria).

Urine osmolality gap

- UOG = (Measured U_{OSM} – calculated [normally expected] U_{OSM}), where

$$\text{Calculated } U_{OSM} = (U_{[Na + K]mmol/L} \times 2 + U_{Urea\ mg/dL}/2.8 + U_{Glucose\ mg/dL}/18)$$

- Normal U_{OSM} gap (UOG) is 10 to 100 mOsm/kg. The UOG accounts for unmeasured NH_4^+ plus other unmeasured cations and their corresponding anions.
- A UOG may be used to estimate NH_4^+ level as UOG/2, that is, NH_4^+ is almost equal to UOG/2. A value greater than 75 mmol/kg suggests normal urine NH_4^+ levels and may be used to rule out RTA.
- With increased NH_4^+ secretion in diarrhea, UOG can exceed 100 mmol/kg.

Conditions with normal SAG metabolic acidosis

Recall SAG = (unmeasured anions$^-$ – unmeasured cations$^+$) ≤ 12 ± 2 mmol/L.

Extrarenal causes of normal SAG metabolic acidosis

- *Diarrhea
- *Ureterosigmoid anastomosis greater than ileal conduit
- Loss of gastrointestinal (GI) fluids with high HCO_3^- content: enteric fistulas, drainage of biliary, pancreatic, or enteric secretions
- D-Lactic acidosis (see also conditions with elevated SAG metabolic acidosis)

- Exogenous sources of acids: hyperalimentation containing acidic amino acids and hydrochloric acid; infusion of NH_4Cl; high volume infusion of normal saline
- *Toluene ingestion (if good kidney function due to rapid excretion of hippurate)
- Drug induced: acetazolamide, topiramate, zonisamide, amphotericin B, K-sparing diuretics, trimethoprim, pentamidine, oral $CaCl_2$ and $MgSO_4$ (Oral $CaCl_2$ and $MgSO_4$ may cause metabolic acidosis because of the formation and loss of calcium or magnesium carbonate in the stool.), cholestyramine (Cholestyramine [cationic resin given as a chloride salt] may form a bicarbonate salt that is eliminated in the stool.)
- Post**hypo**capnia (aka posthypocarbia) metabolic acidosis: Prior renal HCO_3^- loss to compensate for chronic respiratory alkalosis is uncovered as metabolic acidosis following resolution of the hyperventilated state.
- Treatment of DKA with excessive volume repletion resulting in rapid urinary loss of ketone bodies can convert a high SAG to a normal SAG metabolic acidosis, also known as "hyperchloremic metabolic acidosis."
- Renal causes
  - *Renal tubular acidosis
  - Poor overall kidney function with eGFR greater than 15 to 30 mL/min/1.73 m^2

*Special conditions with normal SAG metabolic acidosis are discussed later.

Nonrenal, aka Extrarenal, Causes of Normal SAG Metabolic Acidosis

GI causes

Diarrhea

- Mechanisms of normal SAG metabolic acidosis
  - Intestinal HCO_3^- loss in exchange for Cl^- reabsorption
  - Volume depletion with reduced Na^+ delivery to ENaC limits H^+ secretion.
- Laboratory findings consistent with diarrhea
  - Normal AG metabolic acidosis
  - Negative U_{AG}
  - Increased UOG due to increased NH_4^+ secretion
  - Urine pH is greater than 5.5 despite increased urinary H^+ secretion. This is due to NH_3 buffering from stimulated ammoniagenesis associated with hypokalemia and metabolic acidosis. Of note, urine pH can be low in acute

diarrhea-associated metabolic acidosis or ongoing diarrheal fluid loss where ammoniagenesis is (still) insufficient.

The increased ammoniagenesis in diarrheal states provides a high buffering capacity for urinary H^+. The reduced free H^+ concentration manifests as high urine pH.

$$\uparrow \mathbf{NH_3} + \uparrow \mathbf{H^+} \rightarrow \uparrow NH_4^+ + H^+ \rightarrow \text{urine pH} > 5.5$$

Ureterosigmoid anastomosis, ileal conduit

- Mechanisms for normal AG metabolic acidosis:
  - Intestinal reabsorption of urinary $NH_4^+ + Cl^-$. The reabsorbed NH_4^+ consumes an equimolar HCO_3^- to form urea in the liver.
  - Intestinal reabsorption of urinary Cl^- in exchange for HCO_3^- secretion
- Metabolic acidosis is generally more severe with ureterosigmoid anastomosis than with ileal conduit because of longer urine contact time and greater surface area exposed to the intestine in the former.
- Worsening of metabolic acidosis in patients with either ureterosigmoid anastomosis or ileal conduit should prompt evaluation for distal intestinal or ileal loop obstruction, respectively. The worsened metabolic acidosis could be due to:
  - Resultant urinary obstruction thereby suboptimal renal H^+ secretion
  - Prolonged exposure of intestinal mucosa to urine leads to increased NH_4^+ reabsorption and HCO_3^- wasting via Cl^--HCO_3^- exchanger.

Toluene ingestion

- Patients with good kidney function present with normal SAG metabolic acidosis because toluene metabolites, hippurate and benzoate anions, are freely filtered and excreted. The filtered anions drive the excretion of Na^+ and K^+ cations. This results in a positive U_{AG} because

$$U_{AG} = \uparrow U_{Na} + \uparrow U_K - U_{Cl} > 0$$

- The presence of hippurate/benzoate in the urine also increases urine osmolality. Thus, measured urine osmolality will be much higher than what is normally expected. That is, there will be an increase in UOG, where UOG is defined as:

$$\text{UOG} = (\text{Measured } U_{OSM} - \text{Calculated [normally expected] } U_{OSM})$$

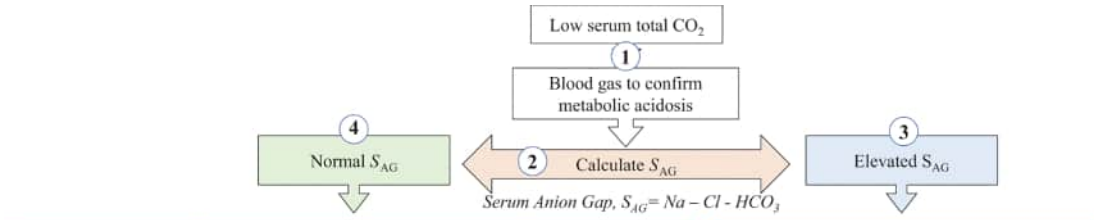
where

$$\text{Calculated } U_{OSM} = (U_{[Na+K]mmol/L} \times 2 + U_{\text{Urea mg/dL}}/2.8 + U_{\text{Glucose mg/dL}}/18)$$

- Normal U_{OSM} gap (UOG) is 10 to 100 mOsm/kg.
- With toluene intoxication, UOG may be greater than 100 to 150 mOsm/kg.

Renal Tubular Acidosis

RTA may be suspected when there is a normal SAG metabolic acidosis, low urine ammonium level, positive U_{AG}, or UOG less than 100 mOsm/kg (**Figure 2.6**).



Differential diagnosis for normal S_{AG} metabolic acidosis	[a]24-h urine NH_4^+ level	Urine AG (U_{AG}) $= U_{Na} + U_K - U_{Cl}$	[b]UOG ÷ 2
Diarrhea Extrarenal loss of pancreatic or biliary secretions [c]Ureteral-gastrointestinal connections	Normal or high	Negative	>75 mmol/kg
Toluene	Normal or high	Positive	>75 mmol/kg
Renal tubular acidosis	Low	Positive	<50 mmol/kg

Differential diagnosis for ↑S_{AG} metabolic acidosis

Methanol (formate)
Metformin (lactate)
Uremia (sulfate, phosphate, urate, etc
Diabetic ketoacidosis (acetoacetate, β-hydroxybutyrate)
Paraldehyde (lactate)
Propylene glycol (lactate)
Pyroglutamate (aka 5-oxoproline) with chronic acetaminophen use
Iron overload (lactate)
Isoniazid (lactate)
Lactic acidosis (lactate)
Ethylene glycol (glycolate, oxalate)
Salicylic acid (salicylate)

FIGURE 2.6 **Evaluation of metabolic acidosis.** 1. Confirm the presence of metabolic acidosis in the presence of a low serum total CO_2. 2. Calculate serum anion gap. 3. Differential diagnosis for elevated serum anion gap is shown in blue box. 4. Differential diagnosis for normal anion gap metabolic acidosis can be further narrowed down by various indices including 24-hour urine NH_4^+ levels, urine anion gap, or urine osmolality gap.

Abbreviations: AG, anion gap; S_{AG}, serum anion gap; U_{Cl}, urine chloride concentration; U_K, urine potassium concentration; U_{Na}, urine sodium concentration; UOG, urine osmolality gap.

[a]Reference normal range for 24 hours of urine ammonium is 15 to 56 mmol (Mayo Medical Laboratories).

[b]Urine osmolal gap (U_{OG}) may be calculated as:

U_{OG} = Measured U_{OSM} – calculated U_{OSM}, where calculated $U_{OSM} = U_{[Na + K]mmol/L} \times 2 + U_{Urea\ mg/dL}/2.8 + U_{Glucose\ mg/dL}/18$

[c]Ureterosigmoidostomy, ileal conduit.

Proximal renal tubular acidosis (pRTA, a.k.a. RTA type 2)

pRTA is caused by impairment of HCO_3^- reabsorption.

Clinical presentation of pRTA

- Serum [HCO_3^-] is typically greater than 15 mmol/L.
- Urine pH varies with serum [HCO_3^-], that is, urine pH is greater than 5.5 if receiving alkalinization therapy, but urine pH will be appropriately low, pH less

than 5.5, in the presence of metabolic acidosis.

- Hypokalemia
- Growth impairment
- Polyuria

Etiologies of pRTA

- To understand the etiologies of pRTA, review normal bicarbonate reabsorption at the proximal tubules (see **Figure 2.1**). Any defect that interferes with normal bicarbonate reabsorption can lead to pRTA.
- Isolated defects:
  - Autosomal dominant pRTA, SCL9A3 gene, encoding NHE3 transporter
  - Autosomal recessive pRTA (SLCA4A4 gene), encoding NBC1: associated with intellectual disability, ocular abnormalities (glaucoma, cataracts, band keratopathy)
  - Sporadic pRTA: nonfamilial, transient type described in infancy due to immaturity of NHE3 function
  - Isolated defects are rare. Typically, pRTA is associated with generalized proximal tubular transport defects (Fanconi syndrome).

NOTE

- Fanconi syndrome refers to multiple proximal tubular transport defects leading to aminoaciduria, glucosuria, uricosuria, and phosphaturia.
- Genetic conditions associated with Fanconi syndrome: cystinosis, galactosemia, tyrosinemia, hereditary fructose intolerance, Lowe syndrome (oculocerebrorenal syndrome), Alport syndrome, Wilson disease, and mitochondrial cytopathies
- Acquired conditions associated with Fanconi syndrome: multiple myeloma, heavy metals, amyloidosis, paroxysmal nocturnal hemoglobinuria, drugs (cisplatin, ifosfamide, aminoglycosides, imatinib, tenofovir, valproate [recall valproate also causes mitochondrial dysfunction and lactic acidosis])

  - Drugs that block carbonic anhydrase II (CA II) activity: acetazolamide and antiepileptic drugs, topiramate and zonisamide; unlike pRTA from other causes where there is no increased stone risk, CA II inhibitor-induced pRTA may be associated with increased calcium phosphate and calcium oxalate stone risk presumably due to reduced citrate excretion.

Diagnosis of pRTA

- Fractional excretion of HCO_3^- ($FeHCO_3$) is greater than 15% and urine pH is typically greater than 7.5 following HCO_3^- load (0.5-1.0 mmol/kg body weight/h to increase serum [HCO_3^-] concentration >20 mmol/L).
- $FeHCO_3 = ([U_{HCO3} \times S_{Cr}] / [P_{HCO3} \times U_{Cr}]) \times 100\%$

Management of pRTA

- Potassium replacement (use K-citrate to treat both hypokalemia and metabolic acidosis)
- Bicarbonate replacement 5 to 15 mmol/kg/d (after *S*[K^+] is at relatively safe range)
- Thiazide diuretics → induces volume contraction → enhances proximal reabsorption of bicarbonate (NOTE: Thiazides can also worsen hypokalemia.)
- Vitamin D and phosphate for patients with rickets and hypophosphatemia

Distal renal tubular acidosis

- dRTA is due to impaired H^+ secretion.
- Etiologies of dRTA: In order to understand the different etiologies of dRTA, review normal H^+ secretion at the CCD (see **Figure 2.2**). Any defect that interferes with normal H^+ secretion can lead to dRTA.
- Metabolic acidosis may be severe; serum [HCO_3^-] may be less than 5 mmol/L.

Normo-, hypokalemic dRTA (aka RTA, type 1)

- Clinical manifestations of dRTA type 1:
  - Urine pH greater than 5.5 due to impaired H^+ secretion
  - Normo- to hypokalemia because K^+ secretion may be increased in the absence of competition with H^+ for the negatively charged lumen.
  - Hypercalciuria, nephrocalcinosis, nephrolithiasis: Chronic metabolic acidosis induced bone resorption, reduced urinary citrate secretion, and high urine pH facilitate calcium phosphate precipitation.
- Conditions associated with dRTA type 1:
  - Isolated defect/mutation of either of the two subunits of apical H^+-ATPase: autosomal recessive mutation, may be associated with progressive sensorineural deafness
  - Isolated defect/autosomal mutation of basolateral Cl^--HCO_3^- exchanger exchange (AE-1)
  - Autoimmune diseases with autoantibodies inhibiting H^+-ATPase trafficking to apical membranes, for example, Sjögren, rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, hypergammaglobulinemia
  - Medications: lithium, toluene (chronic exposure), topiramate, ibuprofen, ifosfamide (more commonly causes pRTA than dRTA), rarely bisphosphonates (zoledronate)
  - Others: medullary sponge kidney, Wilson disease, hypercalcemic conditions

Hyperkalemic dRTA (RTA type 4)

- Clinical manifestations:
  - Hyperkalemic dRTA presents with a urine pH less than 5.5. Hyperkalemia inhibits ammoniagenesis. NH_3 is needed to buffer/facilitate H^+ secretion: $NH_3 + H^+ \rightarrow NH_4^+$. The lack of NH_3 leaves more free H^+ in tubular lumen which lowers urine pH.
  - Patients with dRTA type 4 do not have an increased risk of nephrocalcinosis which is likely due to their low urinary pH and reduced risk for calcium phosphate stones.
- Conditions associated with hyperkalemic dRTA
  - Hyporenin hypoaldosteronism: may be seen in patients with DM
  - Pseudohypoaldosteronism type 1 (ENaC mutation) and type 2 (aka Gordon syndrome, a condition that arises from a number of mutations that result in NaCl cotransporter hyperactivity). See also "Hyperkalemia" section.
  - Medications:
    - ENaC inhibitors: K-sparing diuretics (amiloride, triamterene), trimethoprim, pentamidine
    - Reduced mineralocorticoid activity: inhibitors of the renin-angiotensin-aldosterone system (RAAS), heparin, nonsteroidal anti-inflammatory drugs
    - Increased sodium chloride cotransporter (NCC) activity with resultant reduced Na^+ delivery to ENaC: cyclosporine, tacrolimus
  - Obstructive uropathy affecting transmembrane voltage
  - Miscellaneous: tubulointerstitial nephropathy, sickle cell nephropathy
- Diagnosis of dRTA
  - Administer NH_4Cl (100 mg/kg lean body weight) oral load over 1 hour or a loop diuretic (to increase Na^+ delivery to ENaC) ± mineralocorticoid fludrocortisone.
  - Individuals with normal acid secretion can increase H^+ secretion and lower urine pH, but those with dRTA cannot.
- Management of dRTA
  - Treatment of underlying disease
  - Bicarbonate supplement 1 to 2 mmol/kg lean body weight/d. Caution: Correction of severe hypokalemia must be done PRIOR to alkalinizing therapy in all patients with concurrent hypokalemia and metabolic acidosis to avoid worsening of existing hypokalemia and associated life-threatening arrhythmias.
  - If hyperkalemic in a hypoaldosterone state: Consider fludrocortisone ± furosemide; dietary K^+ restriction may also be necessary.

Mixed RTA (aka type 3)

- Coexistence of both pRTA and dRTA
- Conditions associated with RTA type 3:
  - Mixed RTA may be seen in premature infants and children. This is generally transient and thought to be due to delayed development of tubular acid-base regulation.
  - Mutation of CA II (Guibaud-Vainsel syndrome)
    - Rare, autosomal recessive
    - Coexistence of pRTA and dRTA
    - Failure to maximally acidify urine, decreased NH_4^+ excretion, high urinary citrate level (thought to be due to concurrent proximal tubular dysfunction)
    - Osteopetrosis (increased bone calcification, thick dense bones on plain radiographs) due to failure of osteoclasts to secrete acid to dissolve the bone mineral
    - Cerebral calcification, mental retardation, sensorineural deafness

H^+ back-leak

Amphotericin is a multiplanar lipophilic molecule that can insert itself into the tubular membrane and act as an ionophore allowing urinary H^+ to leak back into tubular cells and circulation. Liposomal formulation of amphotericin essentially covers amphotericin with a lipophobic surface, thereby reducing the drug's ability to insert itself into the cell membrane, thus reducing H^+ back-leak and other electrolyte losses **(Figure 2.7**).

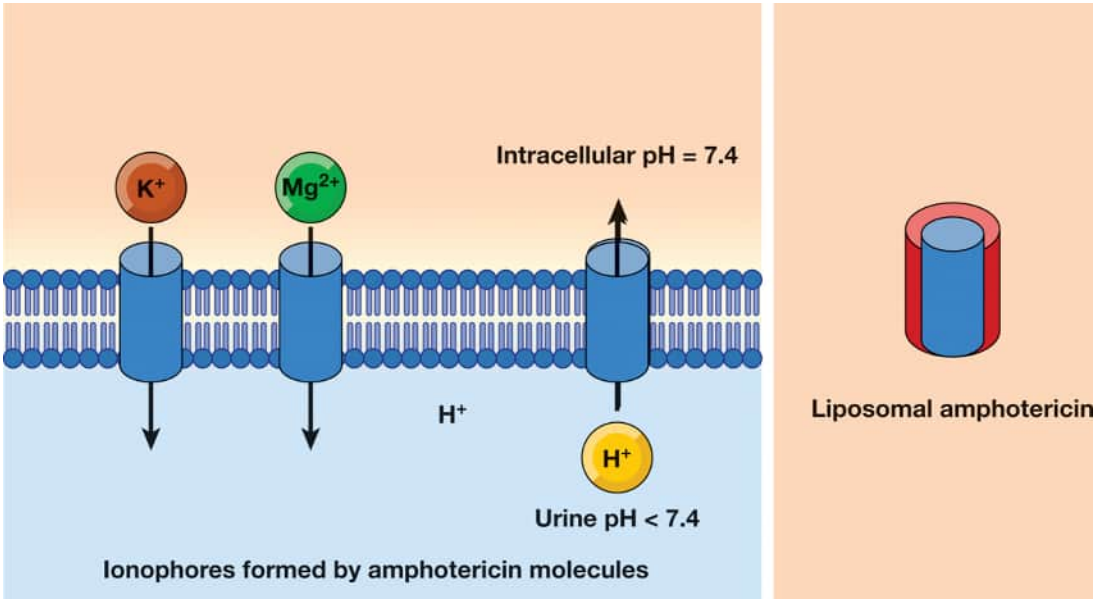


FIGURE 2.7 Amphotericin: metabolic acidosis and electrolyte wasting. Left: The lipophilic multiplanar amphotericin molecule inserts itself into tubular cell membranes to form ionophores (nonspecific electrolyte channels, shown here as blue channels). The direction of electrolyte movement depends on the concentration difference between the intracellular and urinary space. Intracellular concentrations of K^+ and Mg^{2+} are much higher than those in the urine, thus favoring K^+ and Mg^{2+} leakage/wasting into the urine. Urine concentration of H^+, however, is much greater than that intracellularly, which favors H^+ "back-leak" thus the development of metabolic acidosis. Right: The aim of "liposomal" amphotericin formulation is to coat the molecule with a lipophobic layer to minimize its insertion into tubular cell membranes.

Table 2.2 summarizes the different types of RTA.

Table 2.2 Renal tubular acidosis

	Proximal RTA, type 2	Distal RTA, type 1	Distal RTA, type 4	Distal RTA, type 3
Function impaired	HCO_3^- reabsorption	H^+ secretion	H^+ secretion	HCO_3^- reabsorption and H^+ secretion
Associated defects, inhibitors, or loss-of-function mutations	• Sodium hydrogen exchanger (NHE3) • Sodium bicarbonate cotransporter (NBC1) • Carbonic anhydrase II • Fanconi syndrome	• H^+-ATPase • Carbonic anhydrase II • Anion (Cl^--HCO_3^-) exchanger	• Hypoaldosteronism, inhibitors of ENaC • Urinary obstruction	• Carbonic anhydrase II • Premature birth (transient RTA type 3)
Urine pH	• Urine pH correlates with plasma [HCO_3^-]. • Urine pH increases during bicarbonate replacement but can be low in metabolic acidosis.	Urine pH >5.5 due to defective H^+ secretion	• Urine pH ≤5.5 • High plasma [K^+] can reduce ammoniagenesis (↓NH_3), thus lowering the buffering capacity for any H^+ secreted. Unbuffered H^+ reduces urine pH.	Urine pH varies depending on both plasma [HCO_3^-] and plasma [K^+].
Diagnosis (In addition to laboratory findings, genetic	• Serum [HCO_3^-] is typically > 15 mmol/L. • Fractional excretion	• Serum [HCO_3^-] can be severely low (<5 mmol/L).	• Concurrent metabolic acidosis and hyperkalemia • Very low urine NH_4^+	• Clinical manifestations associated with mutation of carbonic

	Proximal RTA, type 2	Distal RTA, type 1	Distal RTA, type 4	Distal RTA, type 3
testing may uncover specific mutations.)	fraction of HCO_3^- > 15% with bicarbonate load	• Serum $[K^+]$ is low or normal. • Low urine NH_4^+ • No increase in urine Pco_2 with HCO_3^- load. • No lowering of urine pH or increase in urine NH_4^+ with loop diuretic ± fludrocortisone.		anhydrase II: osteopetrosis, cerebral calcification, mentally challenged, sensorineural deafness.
Treatment	• High-dose HCO_3^- replacement (15-20 mmol/kg/d) • Potassium replacement • Vitamin D replacement if hypovitaminosis D with Fanconi syndrome	• Low dose HCO_3^- replacement (1-5 mmol/kg/d) • Potassium replacement	• Treat underlying disease. • For hypoaldosteronism: salt supplement + fludrocortisone	Bicarbonate replacement

Abbreviations: ENaC, epithelial sodium channel; RTA, renal tubular acidosis.

Correction of Metabolic Acidosis With Alkalinization

- Calculating HCO_3 deficit:
  - In general,

HCO_3 deficit (mmol) = 0.5 × lean body weight (kg) × (24 − serum HCO_3^-)

- For severe metabolic acidosis,

HCO_3^- deficit (mmol) = (0.4 + 2.6/actual serum HCO_3^-) × lean body weight (kg) × (24 − serum HCO_3^-)

- Caution must be exercised with alkalinization in patients with preexisting CO_2 retention, severe hypokalemia or hypocalcemia, or volume overload.
- Veverimer: an oral nonabsorbed hydrochloric acid binder that is being evaluated to treat chronic kidney disease (CKD)-associated metabolic acidosis

METABOLIC ALKALOSIS

Chloride-Sensitive Metabolic Alkalosis

- Mechanisms of metabolic alkalosis in hypovolemia
  - Reduced glomerular filtration of HCO_3^-
  - Increased Ang II stimulated NHE3 activity in proximal tubules
  - Avid proximal tubular reabsorption of NaCl reduces distal Cl^- delivery required for HCO_3^- exchange via the Cl^--HCO_3^- exchanger (**Figure 2.8**).

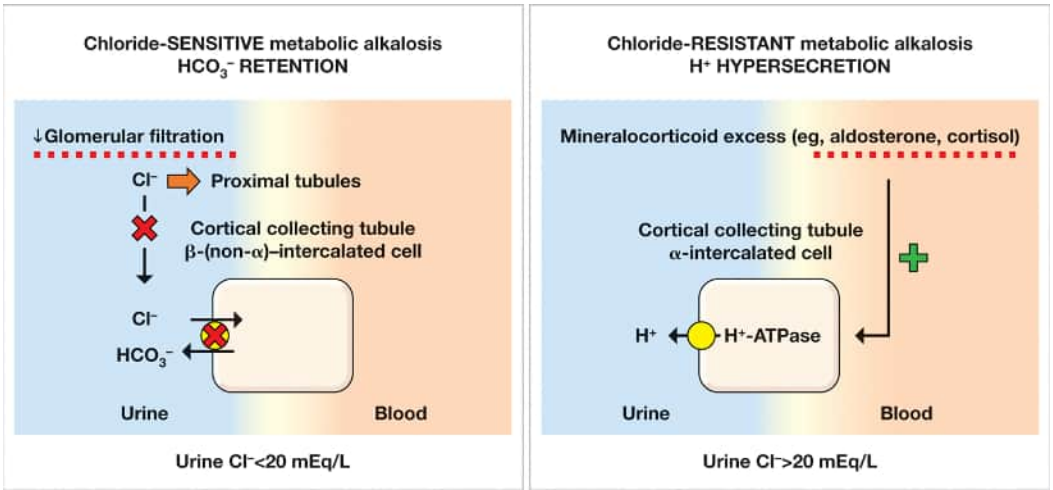


FIGURE 2.8 **Chloride-sensitive versus chloride-resistant metabolic alkalosis.** Left panel: In hypovolemia, most filtered Cl^- are reabsorbed proximally. This leads to reduced distal Cl^- delivery for Cl^--HCO_3^- exchange. The low distal Cl^- delivery is reflected in the low urinary Cl^- concentration. The HCO_3^- retention partly contributes to metabolic alkalosis in volume-depleted states. The infusion of chloride in this case can increase Cl^--HCO_3^- exchange and partly corrects the underlying metabolic alkalosis, hence chloride-sensitive metabolic alkalosis. Right panel: Metabolic alkalosis is driven by mineralocorticoid-stimulated H^+ secretion which has nothing to do with distal Cl^- delivery. Chloride infusion, in this case, does not correct the underlying metabolic alkalosis, hence chloride-resistant metabolic alkalosis. Accordingly, urine Cl^- generally reflects normal chloride intake, which is typically greater than 20 mmol/L.

- Urine studies: Urine Cl^- is low, that is, less than 20 mmol/L, due to avid proximal NaCl reabsorption.
- Treatment: Chloride infusion would increase Cl^--HCO_3^- exchange, increase HCO_3^- secretion, and correct the metabolic alkalosis, hence, "chloride-sensitive" metabolic alkalosis.

Common causes of chloride-sensitive metabolic alkalosis: *vomiting, nasogastric suction, gastrocystoplasty for bladder augmentation, *diuretics, loss of acidic fluid from lower GI tract in patients with villous adenoma or congenital

chloridorrhea, *post**hyper**capnia (recovery from chronic hypercapnia), low dietary chloride intake.

*Selected Conditions Presenting With Chloride-Sensitive Metabolic Alkalosis

Vomiting

- The loss of H^+ in the vomitus (~100 mmol/L) is equivalent to "HCO_3^- loading."
- Severe metabolic alkalosis with serum [HCO_3^-] greater than 45 mmol/L is almost always due to gastric cause. The use of proton pump inhibitors or histamine type 2 (H_2) blockers may reduce gastric H^+ loss and partly ameliorate vomiting or nasogastric drainage-induced metabolic alkalosis.
- There are three phases of vomiting (**Table 2.3**):

Table 2.3 Urine studies in different phases of vomiting

	Acute phase	Later phase	Post-vomiting
Physiologic changes	Acute phase: The high HCO_3^- load leads to increased glomerular filtration of HCO_3^- and accompanying losses of the cations Na^+ and K^+.	Later phase: Once vomiting stops, all HCO_3^- load has been filtered, the patient becomes hypovolemic.	Post-vomiting: In the unsupported patient without fluid and electrolyte repletion, urine Na^+, Cl^-, and K^+ would all be low. At the equilibrium state when bicarbonaturia stops, urine pH becomes low.
Urine Na^+	High	Low (hypovolemia, no more HCO_3^- filtered)	Low
Urine Cl^-	Low (hypovolemia)	Low (hypovolemia)	Low
Urine K^+	High	High (high aldosterone state due to hypovolemia)	Low
Urine pH	High (high filtered HCO_3^- load)	Low (no more HCO_3^- filtered)	Low

- Acute phase: The high HCO_3^- load leads to increased glomerular filtration of HCO_3^- and accompanying losses of the cations Na^+ and K^+.
  - Urine Na^+ is high even in the presence of hypovolemia.
  - Urine K^+ is also high in the presence of the high HCO_3^- load in the tubular lumen.
  - Urine Cl^-, however, would be low as expected for the hypovolemic state.

- Urine pH is high because of the filtered HCO_3^- load.

- Later phase: Once the vomiting stops, all the HCO_3^- load has been filtered, and the patient becomes hypovolemic:
  - Both Na^+ and Cl^- would be low.
  - Aldosterone is stimulated in the hypovolemic state, which drives K^+ and H^+ secretion.
  - Urine K^+ concentration would be high.
  - Urine pH can be low.
- Post-vomiting: In the unsupported patient without fluid and electrolyte repletion, urine Na^+, Cl^-, and K^+ would all be low. At the equilibrium state when bicarbonaturia stops, urine pH becomes low.

NOTE

Hypokalemia in vomiting is predominantly due to renal NOT gastric K^+ loss. Vomitus only contains 10 to 15 mmol/L.

Surreptitious vomiting

Concurrent urine [Cl^-] less than 10 mmol/L and hypokalemia in an emaciated individual should raise concerns for surreptitious vomiting.

Chloride-rich diarrhea (Figure 2.9)

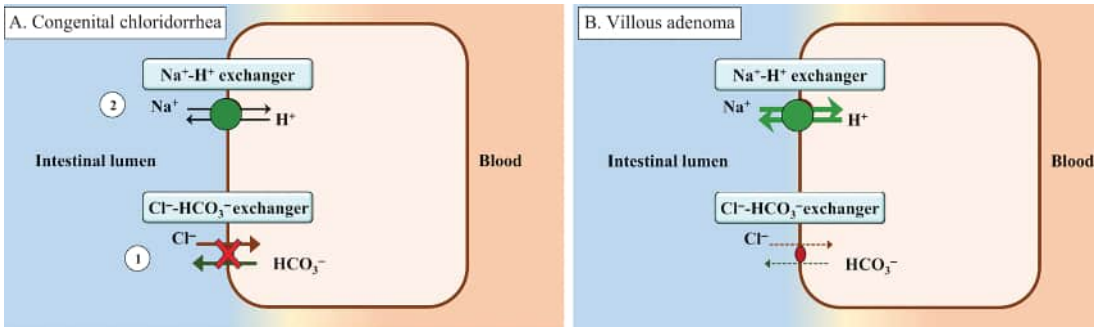


FIGURE 2.9 NaCl absorption coupling with H^+ and HCO_3^- secretion in the gastrointestinal tract. A. In congenital chloridorrhea, loss-of-function mutation of the Cl^--HCO_3^- anion exchanger results in metabolic alkalosis because (1) HCO_3^- cannot be secreted into diarrheal fluid while (2) the intact Na^+-H^+ exchanger continues to function to secrete H^+ as NH_4Cl. B. In villous adenoma, metabolic alkalosis is thought to occur because Na^+-H^+ exchanger function exceeds that of the Cl^--HCO_3^- exchanger.

- Congenital chloridorrhea: Autosomal recessive mutation of the Cl^--HCO_3^- anion exchanger in ileal and colonic mucosa leads to severe Cl^--rich diarrhea

and Cl^--sensitive metabolic alkalosis.

- Villous adenoma: Patients may present with metabolic alkalosis due to an imbalance in function between Na^+/H^+ and Cl^-/HCO_3^- exchangers, where Na^+/H^+ function exceeds that of Cl^-/HCO_3^- exchanger, resulting in net acid secretion (as NH_4Cl) into the diarrheal fluid.

Posthypercapnia

Chronic hypercapnia (chronic CO_2 retention) leads to compensatory renal HCO_3^- retention in exchange for Cl^- to maintain optimal acid-base status. The acute correction of hypercapnia (eg, with acute mechanical ventilation) leaves behind the residual compensatory high serum HCO_3^- and low Cl^- state, which is seen as chloride-sensitive metabolic alkalosis.

Diuretics

Increased Na^+ delivery to CNs and collecting tubules with the use of loop or thiazide diuretics increase Na^+ entry into ENaC, thereby stimulating K^+ and H^+ secretion, leading to hypokalemia and metabolic alkalosis, respectively. Upregulation of RAAS, that is, aldosterone with diuretic use, further promotes this process. Ang II also stimulates NHE3 at proximal tubules, thereby enhancing proximal tubular HCO_3^- reabsorption. Bartter and Gitelman syndromes (BS and GS) are conditions that mimic the effects of loop and thiazide diuretics, respectively, and manifest similar acid-base and electrolyte disturbances. See also "Hypokalemia" section.

Surreptitious diuretic use

Patients may present with metabolic alkalosis and temporally varying, but parallel, urinary Na^+ and Cl^- concentrations (either both very low <20 mmol/L or both very high >>20 mmol/L) due to intermittent use of diuretics.

Chloride-Resistant Metabolic Alkalosis

- This is predominantly due to hypersecretion of acid (H^+) or causes other than reduced Cl^--HCO_3^- exchanger activity (see **Figure 2.8**).
- This form of metabolic alkalosis is not due to the lack of distal urinary Cl^- delivery seen in chloride-sensitive metabolic alkalosis. Urine chloride is thus expected to reflect dietary chloride intake, which is typically greater than 20 mmol/L.
- Chloride infusion in this condition would not correct the metabolic alkalosis, hence "chloride-resistant" metabolic alkalosis.

- Common causes of chloride-resistant metabolic alkalosis are discussed below.

Mineralocorticoid excess

- Direct effect: increased H^+ secretion from α-IC in collecting duct (CD)
- Indirect effect: increased ENaC activity resulting in negative luminal charge generation and facilitated H^+ secretion

Glucocorticoid excess

- Increases NHE3 activity and expression and activity of NBC1 in proximal tubules

Exogenous alkali

- Sources: crack cocaine with alkali load, citrate from transfusion products or regional anticoagulation used in CKRT, transplacental transfer from mother with metabolic alkalosis, excessive calcium carbonate ingestion
- In contrast to milk-alkali syndrome where serum phosphorus may be normal to high (from milk), calcium-carbonate-induced metabolic alkalosis may be associated with low serum phosphorus due to its phosphorus-binding effect. The latter is also known as "calcium-alkali syndrome."
- The combined use of polystyrene sulfonate (Kayexalate) and either aluminum or magnesium hydroxide or calcium carbonate may result in bicarbonate generation and absorption. See **Appendix A2.1** if interested in proposed reactions.
- Sodium zirconium cyclosilicate and patiromer may also bind GI H^+/NH_4^+ and increase serum bicarbonate.

Pendred syndrome

- Rare syndrome with mutation of pendrin (Cl^--HCO_3^- exchanger in β-IC in the CD), where patients may present with goiter, sensorineural deafness, and metabolic alkalosis. (Pendrin is also present in the thyroid gland and ear.)
- Clinical characteristics
  - The use of thiazide diuretics in patients with Pendred syndrome can precipitate severe hypovolemia, metabolic alkalosis, and hypokalemia. See **Appendix A2.2** for mechanisms.
  - Pendrin expression has been shown to be downregulated by acetazolamide. Combined use of thiazides and acetazolamide may synergistically induce significant diuresis.

Cystic fibrosis

- HCO_3^- secretion by pendrin is thought to depend on Cl^- recycling via cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel, the defective channel in cystic fibrosis.
- Patients with cystic fibrosis are at increased risk of developing metabolic alkalosis.

Other Causes of Metabolic Alkalosis

Metabolic alkalosis associated with electrolyte disturbances

- Severe hypokalemia
  - Increases ammoniagenesis, thereby facilitating H^+ secretion
  - Increases H^+ secretion via increasing NHE3 and sodium bicarbonate exchanger activities in proximal tubules
  - Reduces NKCC2 activity, thereby increasing sodium delivery to ENaC, which generates a negatively charged lumen, and facilitates H^+ secretion
  - Increases H^+-K^+-ATPase activity in CD
  - Reduces pendrin expression and activity in β-IC in CD
- Hypomagnesemia may present with metabolic alkalosis via associated hypokalemia.
- Hypercalcemia blocks ROMK, which indirectly blocks NKCC2 to cause metabolic alkalosis.

Refeeding metabolic alkalosis

- Mechanism unknown, thought to be a rebound process following SKA. Avid NaCl retention post-feeding may also play a role in maintaining chloride-sensitive metabolic alkalosis.
- This condition self-resolves.

Table 2.4 summarizes diagnostic testing for common conditions that present with metabolic alkalosis.

Table 2.4 Evaluation of metabolic alkalosis

	Urine Na^+ (mmol/L)	Urine Cl^- (mmol/L)	Interpretation	Urine pH	Differential diagnosis
Hypovolemia	Low <20	Low <20	—	—	Hypovolemia

	Urine Na^+ (mmol/L)	Urine Cl^- (mmol/L)	Interpretation	Urine pH	Differential diagnosis
	High >20	Low <20	$U_{Na} \gg U_{Cl}$, suggests the presence of anions other than chloride. These anions could be **bicarbonate** or **nonreabsorbable anions**.	**High urine pH (>6.5)** suggests the presence of high bicarbonate in the urine.	**Bicarbonaturia** from excess serum bicarbonate generation Acute vomiting Nasogastric suction Congenital chloridorrhea Villous adenoma
				Low urine pH (≤6.5) suggests low bicarbonate in the urine, which implies the anion in question is a nonreabsorbable anion.	**Nonreabsorbable anion** Antibiotics Ketoacids
	High >20	High >20	High U_{Na} and high U_{Cl} suggest conditions with ongoing renal salt loss that lead to metabolic alkalosis.	—	Current diuretic use Electrolyte disturbances that can have diuretic effect (hypercalcemia, hypomagnesemia). Bartter and Gitelman syndromes Cystic fibrosis

	Urine Na^+ (mmol/L)	Urine Cl^- (mmol/L)	Interpretation	PRA and plasma aldosterone	Differential diagnosis
Euvolemia	High >20	High >20	Concurrent high U_{Na} and U_{Cl} are consistent with a euvolemic or hypervolemic state where there is overactive H^+ secretion leading to metabolic alkalosis. This occurs with hyperfunctioning	High plasma aldosterone level and low PRA	Primary adrenal hyperplasia or tumors Glucocorticoid remediable aldosteronism

	Urine Na^+ (mmol/L)	Urine Cl^- (mmol/L)	Interpretation	Urine pH	Differential diagnosis
			ENaC (eg, Liddle syndrome) or increased mineralocorticoid activity (eg, increased aldosterone level or increased level of any molecule with mineralocorticoid activity or gain-of-function mutation of mineralocorticoid receptor [Geller syndrome]).	Normal or low PRA and normal or low plasma aldosterone level	Renovascular HTN (eg, renal artery stenosis, FMD, malignant HTN, scleroderma, renal vasculitis) Renin secreting tumors
				High PRA and plasma aldosterone level	Liddle syndrome Cushing Licorice ingestion Apparent mineralocorticoid excess Congenital adrenal hyperplasia Chrousos syndrome Geller syndrome

Abbreviations: ENaC, epithelial sodium channel; FMD, fibromuscular dysplasia; HTN, hypertension; PRA, plasma renin activity.

Management of Metabolic Alkalosis

Severe metabolic alkalosis (serum HCO_3^- [total CO_2] >45 mmol/L or with pH ≥7.5) is not well tolerated due to associated hypokalemia, hypocalcemia (reduced ionized calcium), ± hypophosphatemia (not as severe as that seen with acute respiratory alkalosis), arrhythmias, hypoxemia (due to compensatory pulmonary hypoventilation), myocardial and cerebral ischemia.

Indications for aggressive therapy

- Underlying lung disease (eg, chronic CO_2 retainers) with acute respiratory decompensation
- Myocardial or cerebral ischemia

Treatment options

- Treat underlying etiology whenever applicable.
- Optimize volume status with chloride-containing solution whenever applicable.

- Treat hypokalemia with KCl (use Cl^- formulation to enhance HCO_3^- secretion). Hypokalemia must be treated because it maintains metabolic alkalosis via enhancing H^+ secretion.
- Evaluate and treat hypomagnesemia and hypercalcemia.
- Consider H_2-blockers or proton pump inhibitors for gastric fluid loss.
- Acetazolamide:
  - Consider acetazolamide in patients with both volume overload and hypoventilation.
  - Adverse effects of acetazolamide: Although acetazolamide stimulates respiratory drive via inducing metabolic acidosis, its use can lead to hypercapnia because RBC uptake of CO_2 from peripheral tissues and uptake of RBC CO_2 by alveoli require carbonic anhydrase. CO_2 retention can occur and cause respiratory acidosis and a drop in pH. Other adverse effects: hypokalemia, hypophosphatemia, metabolic acidosis, transaminitis, acute tubulointerstitial nephritis
- Acidification:
  - Possible solutions (NH_4Cl, HCl, or arginine HCl)
  - Quantity of H^+ (mmol) needed to correct severe refractory metabolic alkalosis
    - = HCO_3^- excess (mmol) = 0.5 × lean body weight (kg) × (serum HCO_3^- – 24), for female
    - = HCO_3^- excess (mmol) = 0.6 × lean body weight (kg) × (serum HCO_3^- – 24), for male
- Kidney replacement therapy with the use of bicarbonate-free replacement fluid may be considered in patients with kidney failure.

RESPIRATORY ALKALOSIS

- Common causes: pneumonia; pulmonary embolism; head trauma; hyperthyroidism; pregnancy; cirrhosis; living at high altitude; early bacterial sepsis (gram positive or negative organism); meningitis; drugs (theophylline, salicylate); myocardial infarction; atrial fibrillation, flutter, tachycardia
- Acute respiratory alkalosis is associated with severe hypophosphatemia due to rapid intracellular phosphate shift.

RESPIRATORY ACIDOSIS

- Common causes: chronic obstructive pulmonary disease, obstructive sleep apnea, obesity-hypoventilation syndrome, neuromuscular weakness or chest

wall/diaphragm abnormality, central nervous system depression: (drugs or lesions), hypothyroidism, and laryngeal/tracheal stenosis

POTASSIUM

Potassium Background

- Total body K^+ stores in adults: approximately 3,000 to 4,000 mmol (50-55 mmol/kg body weight)
- Unlike Na^+, 98% of K^+ is intracellular. Intracellular K^+ concentration is approximately 140 mmol/L whereas plasma K^+ is approximately 4 to 4.5 mmol/L. Intracellular K^+ content is approximately 3,000 mmol in muscles, 200 mmol in RBCs, and 200 mmol in the liver.
- The optimal plasma K^+ level is between 4.1 and 4.7 mmol/L.
  - U-shaped relationship between serum K^+ and mortality: Ranges below 3.5 or greater than 5.5 mmol/L may be associated with worse all-cause mortality in both hospitalized and ambulatory patients with hypertension (HTN).
  - In patients with CKD, hyperkalemia is much more tolerable compared to those without CKD. A serum K^+ range of 5.5 to 6.0 mmol/L in patients with CKD is associated with lower mortality compared with those in the 3.5 to 3.9 mmol/L range.
- Functions of K^+:
  - Cell metabolism, regulation of protein and glycogen synthesis
  - Major determinant of resting membrane potential that is necessary for action potential generation required for neuromuscular function

Potassium Homeostasis

The initial acute response to a K^+ load is intracellular uptake, a process facilitated by catecholamines and insulin. Renal elimination of K^+ occurs over the next 6 to 8 hours.

Major determinants of plasma K^+ ($P[K^+]$) concentration and total body content

Input: blood transfusions, dietary (salt substitutes [KCl], K^+-containing foods or medications), oral or intravenous supplements. Ninety percent of potassium ingestion is absorbed passively in small intestines with a minor amount absorbed via colonic H^+-K^+-ATPase.

Output: skin (sweats, extensive burns), respiratory (airway secretions), GI tract (5% of dietary intake is excreted in stool), renal excretion (95% of dietary

intake). GI K^+ secretion may occur via colonic Big-K^+ (BK) channels, a process suggested to be upregulated in end-stage kidney disease.

Cellular K^+ shift (**Figure 2.10**)

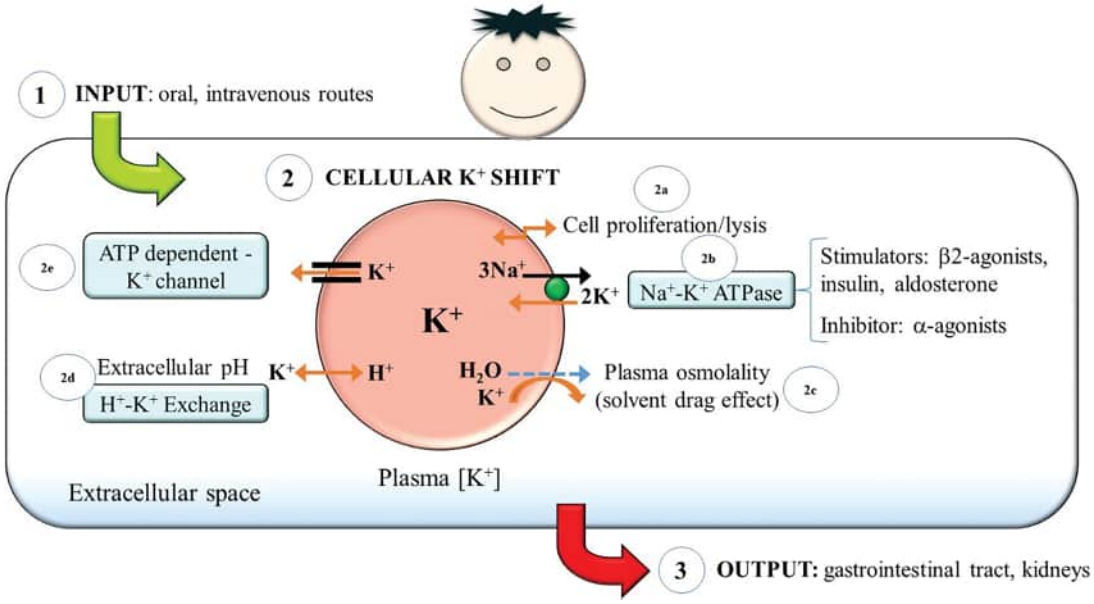


FIGURE 2.10 **Determinants of plasma K^+ concentration.** Plasma potassium concentration is determined by K^+ input, cellular shift, and output. 1. Input: oral ingestion or intravenous supplement of K^+-containing substances. 2. Cellular shift can be determined by a. cell proliferation or lysis, with K^+ intracellular shift in the former and extracellular shift in the latter; b. K^+ uptake via $3Na^+$-$2K^+$-ATPase: this is upregulated by insulin, β2-agonists, and aldosterone. Aldosterone activates Na^+-H^+ exchanger (NHE1) in muscle cells which in turn activates $3Na^+$-$2K^+$-ATPase; α-agonists are inhibitory to $3Na^+$-$2K^+$-ATPase; c. acute increase in plasma osmolality drives extracellular water shift which "drags" K^+ extracellularly, known as the "solvent drag" effect; d. reduced plasma pH can lead to cellular H^+ uptake and an equivalent K^+ efflux while increased plasma pH leads to the reverse; e. ATP keeps the ATP-dependent K^+ channel closed. The lack of ATP opens the channel, allowing K^+ efflux. 3. Output: gastrointestinal tract and kidneys.

- Effect of pH, acid-base status on cellular shift:
  - Low extracellular pH can cause an apparent 1:1 intracellular H^+ and extracellular K^+ exchange and vice versa for high extracellular pH. For readers interested in the mechanism, refer to **Appendix A2.3**.
  - This effect is most pronounced with inorganic metabolic acidosis and less so with organic acidosis (carbon-containing acids, eg, LA, ketoacid), metabolic alkalosis, and respiratory acidosis/alkalosis.
- Effect of acid-base disturbances on renal K^+ excretion:
  - In general, alkalemia stimulates distal renal K^+ secretion, with a greater effect seen in metabolic compared with respiratory alkalosis. Increased intracellular pH increases the activities of ENaC, ROMK, and BK.

    - Respiratory alkalosis also increases K^+ secretion in parallel to the compensatory HCO_3^- secretion.
    - Respiratory acidosis minimally affects renal K^+ secretion.
- Plasma K^+ concentration: Bidirectional passive movement across cells depends on acute changes in plasma K^+ concentrations.
- Extracellular osmolality: Hyperosmolality shifts water out of cells which leads to:
    - Higher intracellular K^+ concentration, hence more favorable gradient for K^+ exit into plasma
    - Extracellular K^+ shift due to solvent drag effect
- $3Na^+$-$2K^+$-ATPase (often denoted as Na^+-K^+-ATPase)
    - Stimulated by insulin, aldosterone, β2-agonists (eg, drug-induced cellular K^+ uptake thus hypokalemia: albuterol, tocolytic agents [ritodrine, terbutaline], dobutamine, isoproterenol, heroin contaminated with clenbuterol)
    - Inhibited by α-agonists, presumably via inhibition of renin release, thus downstream hypoaldosteronism and hyperkalemia
    - Na^+-H^+ exchanger (NHE1) in muscle cells: Aldosterone stimulates Na^+ entry into muscle cells via NHE1. The increased intracellular Na^+ in turn increases intracellular K^+ uptake via increased Na^+-K^+-ATPase activity.
- Others: Xanthine (eg, caffeine, theophylline) can increase K^+ cellular uptake, while glucagon may cause extracellular K^+ shift.

NOTE

- α-Agonists are vasoconstrictive agents such as phenylephedrine and norepinephrine. These agents may cause hyperkalemia in at-risk individuals.
- Dopamine has weak to moderate α-1 activity and could contribute to a minimal increase in $S[K^+]$ if used at high doses.
- Epinephrine has strong α-1 but also moderate β-2 adrenergic activities. Simultaneous infusion of epinephrine with K^+ has been shown to improve K^+ tolerance, presumably via β-2-induced increased cellular uptake.

- ATP-sensitive K^+ channels (KATP):
    - The main regulator of KATP is the ATP/ADP ratio. An elevated ratio (in the presence of Mg^{2+}) leads to channel closure while a reduced ratio opens the channel. KATP closure inhibits K^+ efflux extracellularly.
    - Exercise: ATP depletion during exercise opens up KATP and allows for extracellular K^+ shift. The local increase in K^+ concentration enhances

vasodilatation, hence blood flow to exercising muscles. This effect is impaired with K^+ depletion.

- Cell lysis: Cellular K^+ release into plasma: tumor lysis, rhabdomyolysis, hemolysis, bowel infarction
- Cell proliferation/anabolism: K^+ uptake for cell production (ie, RBCs, platelets) with folic acid or vitamin B_{12} therapy for megaloblastic anemia; refeeding syndrome

Renal Potassium Handling (Figure 2.11)

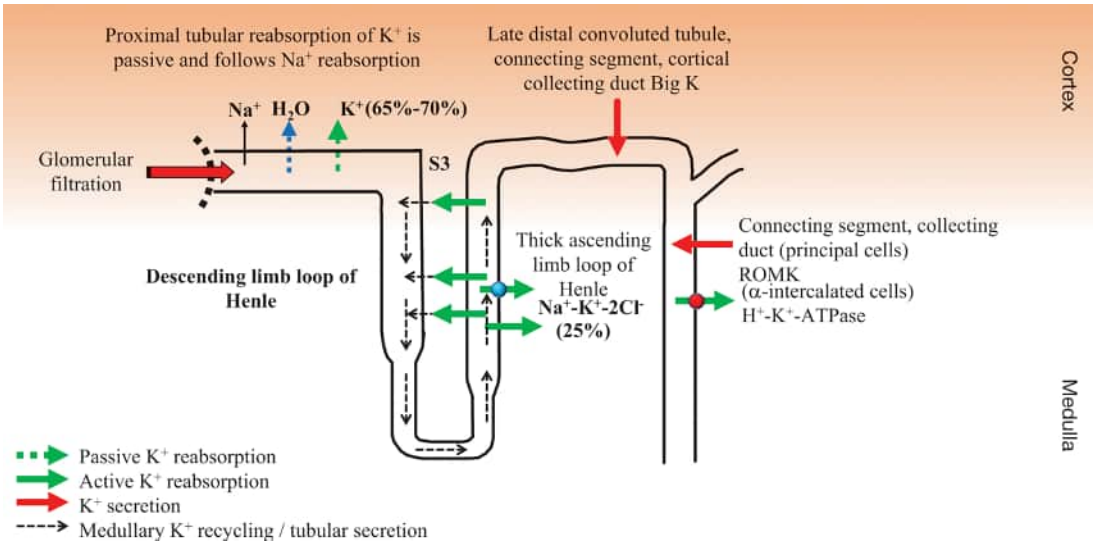


FIGURE 2.11 **Renal potassium handling.**

Kidneys maintain balanced plasma K^+ concentration via regulated K^+ reabsorption and secretion.

K^+ reabsorption

- Proximal tubules: passive paracellular reabsorption in parallel with Na^+ and water
- TAL: active reabsorption via Na^+-K^+-$2Cl^-$ as well as passive paracellular reabsorption
- Cortical and outer medullary CD α-ICs H^+-K^+-ATPase
  - Activity of H^+-K^+-ATPase is increased with K^+ depletion, increased mineralocorticoid activity (eg, aldosterone), and increased progesterone (to retain K^+ during pregnancy).
  - Activity of H^+-K^+-ATPase is reduced with high plasma K^+.

K^+ secretion

Medullary K^+ recycling

- Reabsorbed medullary K^+ is secreted back into the lumen at the S3 segment of the late proximal tubules and the descending limb of the loop of Henle, and is subsequently reabsorbed at the TAL.
- Maintenance of high medullary K^+ concentration is thought to minimize passive K^+-back-leak.

Regulated K^+ secretion

Regulated K+ secretion occurs via ROMK, Kir 4.1, Maxi-K^+ channel, and K^+-Cl^- cotransporter.

- Apical ROMK (see **Figure 2.2**):
  - K^+ secretion via ROMK occurs sequentially as follows:
    1. Na^+ is delivered to ASDN segment including the late distal convoluted tubule (DCT), CN, and CCD. Aldosterone upregulates the expression of ENaC and Na^+-K^+-ATPase and increases ROMK activity, thus enhancing K^+ secretion.
    2. The delivered Na^+ is reabsorbed via apical ENaCs into principal cells. This generates a negatively charged lumen.
    3. The intracellular Na^+ is subsequently reabsorbed in exchange for cellular K^+ uptake via basolateral Na^+-K^+-ATPase.
    4. The accumulated intracellular K^+ within principal cells exits into tubular lumen via ROMK, a movement driven by the favorable electrochemical gradient generated by Na^+ uptake via ENaC.
    5. A good tubular flow is necessary to maintain the favorable electrochemical gradient for continuing K^+ secretion. In addition, a high tubular flow may also stimulate ENaC, thereby enhancing K^+ secretion via the mechanisms outlined earlier.
  - Factors affecting K^+ secretion via ROMK are detailed according to the steps outlined earlier:
    1. Distal Na^+ delivery to ASDN
       a. Availability of Na^+ that can be delivered to ASDN
       b. Presence of aldosterone
       c. Normal functioning mineralocorticoid (aldosterone) receptor
    2. Intact apical ENaC
    3. Intact basolateral Na^+-K^+-ATPase
    4. Intact ROMK
    5. Good tubular flow, that is, volume status; urinary obstruction can affect tubular flow.

6. Others: ADH (thought to increase the number of luminal ROMK channels), adequate functioning nephron mass (eGFR typically >15-20 mL/min/1.73 m^2)

- Kir 4.1/5.1
  - Kir 4.1/5.1 are specialized basolateral K^+ channel in DCT that senses plasma K^+ ($P[K^+]$) and regulates NCC activity.
  - High $P[K^+]$ inhibits the with-no-lysine kinase (WNK), the kinase that normally phosphorylates and activates NCC. Reduced NCC activity allows for increased Na^+ delivery to ENaC, thereby subsequently increasing K^+ secretion. High $P[K^+]$/high K^+ diet have also been shown to stimulate the protein phosphatase PP1A, an enzyme that directly dephosphorylates and inactivates NCC.
  - Low $P[K^+]$ activates WNK activity and NCC, thereby reducing Na^+ delivery to ENaC and effectively reducing kaliuresis (**Figure 2.12**).

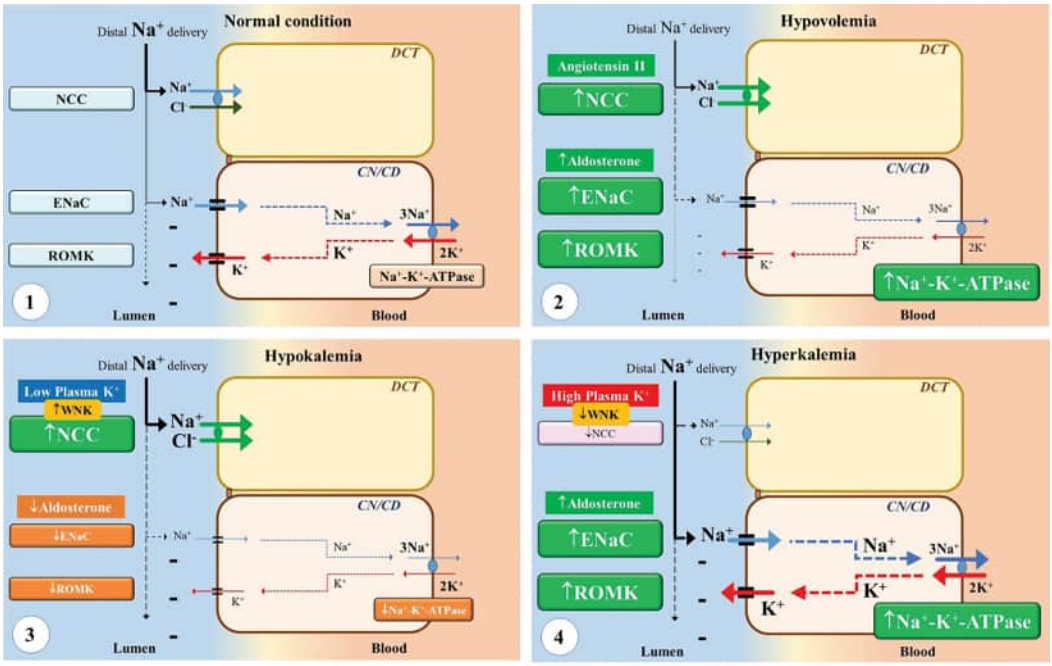


FIGURE 2.12 **Regulation of renal K^+ secretion by plasma K^+ and hypovolemia.** 1. Under normal conditions, Na^+ is delivered to CN/CD enters principal cells via ENaC. The reabsorbed Na^+ is subsequently reabsorbed on the basolateral side in exchange for cellular K^+ uptake via $3Na^+$-$2K^+$-ATPase. The increased intracellular K^+ creates a favorable chemical gradient for K^+ secretion into the lumen. The apical uptake of Na^+ also creates an electronegative lumen that favors the secretion of positively charged K^+ via the renal outer medullary potassium channel (ROMK) and H^+ via H^+-ATPase by α-intercalated cells (not shown). 2. In the hypovolemic state, Ang II stimulates NCC activity, thereby increasing Na^+ reabsorption at DCT. This reduces Na^+ availability for delivery to ENaC, thereby effectively limiting K^+ secretion via ROMK. This explains why there is no K^+ wasting in hypovolemia. 3. Under normal conditions, WNK4 phosphorylates and activates NCC. Hypokalemia reduces

intracellular Cl^-, leaving WNK4 in their Cl-unbound, activated state, to activate NCC. Increased Na^+ entry at NCC reduces Na^+ delivery to ENaC thereby limiting K^+ secretion via ROMK. In addition, hypokalemia inhibits aldosterone which also reduces ENaC, ROMK, and $3Na^+$-$2K^+$-ATPase activities, thus reducing K^+ secretion. 4. High plasma K^+ turns off with-no-lysine kinases 4 (WNK4). Reduced phosphorylation of NCC reduces NaCl reabsorption via NCC, thereby allowing greater Na^+ delivery to ENaC. Not shown here, high $P[K^+]$/high K^+ diet have also been shown to stimulate the protein phosphatase PP1A, an enzyme that directly dephosphorylates and inactivates NCC. Increased Na^+ delivery to ENaC drives greater K^+ secretion at ROMK. In addition, hyperkalemia stimulates aldosterone which upregulates ENaC, ROMK, and $3Na^+$-$2K^+$-ATPase.
Abbreviations: α-IC, α-intercalated cell; Ang II, angiotensin II; CA II, carbonic anhydrase II; CN/CD, connecting segment/collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NCC, sodium chloride cotransporter; ROMK, renal outer medullary potassium channel; WNK, with-no-lysine kinase.

- Apical BK channel aka Maxi-K^+ channel
  - BK is present along the entire nephron but only known to exert its flow-mediated K^+ secretion in DCT and CN/CCD.
  - BK channel is quiescent at basal state but gets activated with increased luminal flow. This explains exaggerated K^+ wasting in patients with high tubular flow (eg, polyuria, diuretics, or BS and GS).
- Apical KCl cotransporter may also play a role in late DCT and CN/CCD K^+ secretion.

Renal [K^+] Secretion in Special Conditions

Hypovolemia

In hypovolemia, most Na^+ are reabsorbed at proximal segments leaving minimal Na^+ delivery to ENaC. In addition, increased Ang II in hypovolemia stimulates NCC. The small remaining amount of Na^+ delivered to ENaC limits K^+ secretion (even in the presence of aldosterone-driven upregulation ENaC, ROMK, and Na-K-ATPase activities associated with hypovolemia).

Primary hyperaldosteronism

Renal K^+ wasting readily occurs because K^+ secretion is not limited by distal Na^+ delivery.

Pregnancy

In pregnancy, K^+ secretion via ROMK and BK are reduced while K^+ reabsorption via H^+-K^+-ATPase is increased in the kidneys to maximally conserve K^+.

HYPERKALEMIA

Clinical Manifestations

- Muscle weakness, cardiac arrhythmias
- ECG changes:
  - Peaked T waves: tall peak (sharp tented) T waves; T wave taller than R wave in 2 or more leads
  - Flattened P waves; prolonged PR interval
  - Changes associated with high risk of cardiac arrest: widened QRS complex; merging of S and T waves; bradycardia, idioventricular rhythm; sine wave formation; ventricular fibrillation

Causes and mechanisms of hyperkalemia are summarized in **Figure 2.13**.

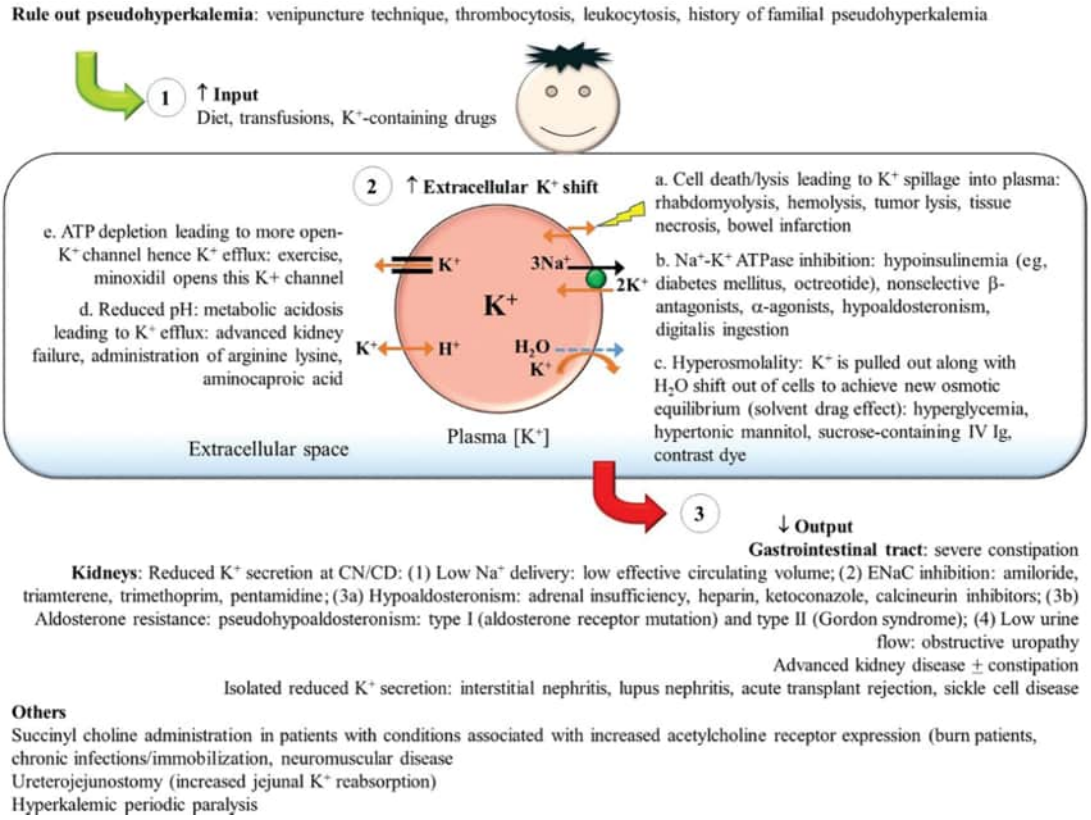

Rule out pseudohyperkalemia: venipuncture technique, thrombocytosis, leukocytosis, history of familial pseudohyperkalemia
1 ↑ Input
Diet, transfusions, K+-containing drugs
2 ↑ Extracellular K+ shift
a. Cell death/lysis leading to K+ spillage into plasma: rhabdomyolysis, hemolysis, tumor lysis, tissue necrosis, bowel infarction
b. Na+-K+ ATPase inhibition: hypoinsulinemia (eg, diabetes mellitus, octreotide), nonselective β-antagonists, α-agonists, hypoaldosteronism, digitalis ingestion
c. Hyperosmolality: K+ is pulled out along with H2O shift out of cells to achieve new osmotic equilibrium (solvent drag effect): hyperglycemia, hypertonic mannitol, sucrose-containing IV Ig, contrast dye
e. ATP depletion leading to more open-K+ channel hence K+ efflux: exercise, minoxidil opens this K+ channel
d. Reduced pH: metabolic acidosis leading to K+ efflux: advanced kidney failure, administration of arginine lysine, aminocaproic acid
K+
3Na+
2K+
H+
H2O
Extracellular space
Plasma [K+]
3 ↓ Output
Gastrointestinal tract: severe constipation
Kidneys: Reduced K+ secretion at CN/CD: (1) Low Na+ delivery: low effective circulating volume; (2) ENaC inhibition: amiloride, triamterene, trimethoprim, pentamidine; (3a) Hypoaldosteronism: adrenal insufficiency, heparin, ketoconazole, calcineurin inhibitors; (3b) Aldosterone resistance: pseudohypoaldosteronism: type I (aldosterone receptor mutation) and type II (Gordon syndrome); (4) Low urine flow: obstructive uropathy
Advanced kidney disease ± constipation
Isolated reduced K+ secretion: interstitial nephritis, lupus nephritis, acute transplant rejection, sickle cell disease
Others
Succinyl choline administration in patients with conditions associated with increased acetylcholine receptor expression (burn patients, chronic infections/immobilization, neuromuscular disease
Ureterojejunostomy (increased jejunal K+ reabsorption)
Hyperkalemic periodic paralysis

FIGURE 2.13 **Causes of hyperkalemia.**

Pseudohyperkalemia

- Refers to in vitro (test tube) not in vivo hyperkalemia
- Treatment is not necessary.
- Conditions associated with pseudohyperkalemia:
  - Excessive fist clinching with blood draw: Exercising (of hand) reduces local ATP and opens up KATP allowing extracellular K^+ shift.
  - Mechanical trauma, hemolysis during blood draw can cause K^+ release extracellularly.

- Thrombocytosis, for example, for every 100,000 platelets/μL, serum K^+ can increase by approximately 0.15 mmol/L because K^+ moves out of platelets after clotting has occurred in a test tube. Diagnosis: Obtain *P*[K^+] (ie, [K^+] measured from a blood sample collected in a heparin-containing tube to avoid clotting process). If serum [K^+] (ie, [K^+] measured in non-anticoagulated blood) is greater than *P*[K^+], that is, *S*[K^+] – *P*[K^+] greater than 0.3 mmol/L, pseudohyperkalemia is likely present.
- Erythrocytosis and leukocytosis (typically >70,000/cm^3), with exception below.
- "Reverse" pseudohyperkalemia in some patients with chronic lymphocytic leukemia:
  - Condition where *P*[K^+] is greater than *S*[K^+] (not the usual *S*[K^+] > *P*[K^+]) due to cell fragility and lysis with centrifugation, traumatic blood handling (shuttling pneumatic tube system) ± heparin-induced K^+ leakage from white blood cells
  - To minimize cell lysis, hand-carry the specimen to the lab immediately after the blood draw and avoid using heparin-containing tubes.
- Benign familial (autosomal dominant) pseudohyperkalemia ± associated stomatocytosis: Passive K^+ leaks from RBCs into serum when the blood sample is left at room temperature. Diagnosis: Serial *S*[K^+] measurements while blood is allowed to cool to room temperature become increasingly high.

Increased K^+ input

- Dietary: K^+-containing foods, salt substitutes (NaCl is replaced for KCl), mixed fruit juices
- K^+-containing medications: KCl, high-dose penicillin-K, K-citrate, polycitrate
- Supplements: fruit/herbal extracts
- RBC transfusion due to K^+ leakage, particularly with massive transfusions or transfusions of prolonged stored blood

Extracellular K^+ shift

- **Cell death**
  - Tumor lysis, large tissue necrosis (eg, bowel/liver infarction), hemolysis, rhabdomyolysis, muscle injury
  - Rewarming following hypothermia: Hypothermia causes an initial decrease in potassium levels (possibly due to increased Na-K-ATPase activity). However, with hypothermic cardiac arrest, hyperkalemia occurs due to cell

lysis and final depolarization. Hyperkalemia can also occur during rewarming.

- **Extracellular pH**
  - Metabolic acidosis:
    - In general, inorganic acids (eg, HCl and sulfuric acid) but not organic acids (acids that contain carbon, eg, ketoacids) can cause significant K^+ shift.
    - However, organic acidosis due to kidney failure or administration of arginine hydrochloride or aminocaproic acid may cause K^+ shift.
    - Lactic acidosis or ketoacidosis has smaller effect on hyperkalemia, partially due to the concurrent entry of both anion and hydrogen ion into cells via a sodium-organic anion cotransporter, thus eliminating the need for K^+ shifting out of cells to maintain electroneutrality.
  - Respiratory acidosis:

No significant effect on extracellular K^+ shift unless severe and prolonged.

- **Extracellular osmolality**
  - Increased extracellular osmolality (eg, hyperglycemia, sucrose-containing IV immune globulin, radiocontrast media, hypertonic mannitol) shifts K^+ extracellularly because:
    - Extracellular H_2O shift with hyperosmolality increases intracellular K^+ concentration, hence greater concentration gradient favoring extracellular shift.
    - Extracellular H_2O shift drags K^+ along: "solvent drag" effect

> **NOTE**
>
> Hyperkalemia is often observed in fasting blood draws (eg, early morning preoperative blood draw) in patients with type 2 diabetes. This is thought to be due to the lack of endogenous insulin secretion with fasting. To correct this hyperkalemia, administer 5% dextrose (D5) saline solutions ± insulin depending on the degree of hyperglycemia.

- **Altered Na^+-K^+-ATPase activity**
  - Reduced insulin secretion reduces Na^+-K^+-ATPase activity.
    - DM (poorly controlled)
    - Somatostatin or somatostatin agonist (octreotide) can lead to a fall in insulin and hyperkalemia in susceptible individuals.
  - Reduced β-2 adrenergic activity by β-blockers reduces Na^+-K^+-ATPase activity.

- β-1 antagonism inhibits catecholamine-stimulated renin release, hence aldosterone.
- β-2 antagonism inhibits Na^+-K^+-ATPase activity.
- Nonselective β-blockers may cause more hyperkalemia compared with β-1 selective antagonists.

Nonselective β-antagonists: alprenolol, bucindolol, carteolol, carvedilol (+α-antagonism), labetalol (+α-antagonism), nadolol, penbutolol, pindolol, propranolol, timolol
Selective β-1 antagonists: acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol

- Inhibition of Na^+-K^+-ATPase: digitalis overdose (digoxin, ingestion of common oleander or yellow oleander)
- **ATP-sensitive K^+ channels**: Opening of K^+ channels leads to K^+ efflux.
  - Lack of ATP as seen during exercise
  - Medications: calcineurin inhibitors (cyclosporine, tacrolimus), diazoxide, minoxidil, isoflurane

Reduced K^+ output

- **Gastrointestinal**:
  - Severe constipation limiting gut K^+ secretion in the setting of poor kidney function
  - Ureterojejunostomy: increased absorption of urinary K^+ by jejunum (see also "Metabolic complications with urinary diversions" section).
- **Kidneys**: reduced renal K^+ secretion
  - Recall renal K^+ secretion depends on (1) distal Na^+ delivery, (2) generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in CN and CD, (3) distal urine flow, (4) presence of aldosterone, (5) functioning MR, (6) kidney mass/function.
  - Problems with any of factors 1 to 6 outlined earlier can cause hyperkalemia (Study **Table 2.5**).

Table 2.5 Etiologies of hyperkalemia

Factors involved in normal renal K^+ secretion	Corresponding problems that may contribute to reduced renal K^+ secretion	Comments
Na^+ delivery to distal segment (connecting/collecting duct)	Reduced Na^+ delivery: low effective circulating volume, hypovolemia Increased NCC activity, thereby leaving less Na^+ delivery to CN/CD: Gordon	Saline infusion would increase renal K^+ secretion. • Gordon syndrome is associated with

Factors involved in normal renal K^+ secretion	Corresponding problems that may contribute to reduced renal K^+ secretion	Comments
	syndrome (aka, familial hyperkalemic hypertension), calcineurin inhibitors (tacrolimus, cyclosporine) Pseudohypoaldosteronism type 1, autosomal recessive (AR PHA1): mutations involving α, β, or γ subunits of ENaC	hypertension, hyperkalemia, and metabolic acidosis. CNI may mimic Gordon syndrome. Treatment: thiazides to block NCC • AR PHA1 affects all organs (lungs, kidneys, colon, sweat and salivary glands). High NaCl content can be seen in sweat. AR PHA1 is more severe the the autosomal dominant form. Treatment: NaCl support + high-dose fludrocortisone
Generation of negative lumen with Na^+ entry via ENaC	Inhibition of ENaC: triamterene, amiloride, trimethoprim, pentamidine	Remove offending agents.
Aldosterone (Aldosterone upregulates ENaC, ROMK, Na-K-ATPase activities, thereby increasing renal K^+ secretion.)	• Hypoaldosteronism: primary adrenal insufficiency • Medications: RAAS inhibitors, NSAIDs, COX-2 inhibitors (prostaglandins normally enhance renin secretion), heparin (including low-molecular-weight heparin), ketoconazole, drospirenone-containing oral contraceptives (eg, Yaz, Yasmin)—drospirenone has mineralocorticoid antagonist activity.	• Remove offending agents. • For primary adrenal insufficiency: hydrocortisone ± fludrocortisone
Mineralocorticoid (aldosterone) receptor	Mineralocorticoid receptor antagonists (spironolactone, eplerenone, finerenone) Pseudohypoaldosteronism type 1, autosomal dominant: mutations involving mineralocorticoid receptor	Remove offending agents Salt support + high-dose fludrocortisone
Good urine flow to maintain the electrochemical gradient for optimal K^+ secretion	Urinary stasis: functional or structural obstruction of urinary collecting system (eg, benign prostate hypertrophy, neurogenic bladder, extrinsic tumor compression of collecting system)	• Correct underlying structural problem. • Consider α-antagonists for benign prostate hypertrophy, neurogenic bladder
Kidney mass/function	Kidney failure: • Reduced overall capacity for renal K^+ secretion	• Treat any associated acidemia. • Ensure regular bowel movement.

Factors involved in normal renal K^+ secretion	Corresponding problems that may contribute to reduced renal K^+ secretion	Comments
	• Reduced Na^+-K^+-ATPase activity in uremia may reduce cellular uptake.	• Consider gut K^+-binders.

Abbreviations: CN/CD, connecting segment/collecting duct; CNI, chronic nephritic syndrome; COX-2, cyclooxygenase-2; ENaC, epithelial sodium channel; NCC, sodium chloride cotransporter; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; ROMK, renal outer medullary potassium channel.

Selected renal causes of hyperkalemia

Pseudohypoaldosteronism type 2 (Gordon syndrome aka familial hyperkalemic hypertension [FHH]): This condition is due to several mutations that result in the gain-of-function of NCC and is characterized by HTN, hyperkalemia, and metabolic acidosis.

- Responsible mutations:
  - WNK4, L-WNK1: Under normal conditions, WNK kinases phosphorylate Ste20-related proline alanine rich kinase (SPAK), also a kinase, which in turn phosphorylates NCC rendering NCC active. Mutations involving WNKs can result in increased NCC activity.
  - Kelch-like 3 (KLHL3) and Cullin 3 (CUL3): CUL3 and KLHL3 form the CUL3KLHL3 E3 ligase complex whose function is to ubiquitinate WNK isoforms. Ubiquitination is a process whereby proteins are tagged for lysosomal degradation. Mutations that disrupt the formation of this complex's ability to ubiquitinate WNKs can also lead to increased NCC activity.
- How activation of NCC leads to HTN, hyperkalemia, and metabolic acidosis:
  - Activation of NCC increases Na^+ reabsorption at DCT, thereby reducing Na^+ delivery to CN/CD. Reduced Na^+ availability at CN/CD limits K^+ and H^+ secretion, giving rise to hyperkalemia and metabolic acidosis, respectively.
  - The increase in Na^+ and Cl^- reabsorption leads to HTN and volume expanded state, which suppresses the RAAS. Reduced aldosterone also contributes to hyperkalemia and metabolic acidosis.
  - Of interest, calcineurin inhibitors (eg, cyclosporine and tacrolimus) can also increase NCC activity and lead to the triad of HTN, hyperkalemia, and metabolic acidosis.
- Clinical manifestations: HTN in early adulthood, non-AG metabolic acidosis and hyperkalemia ± hypercalciuria, osteoporosis, and nephrolithiasis
- Treatment: dietary sodium restriction and thiazide diuretics to directly inhibit NCC

Miscellaneous causes of hyperkalemia

Hyperkalemic periodic paralysis

- Autosomal dominant, varying penetrance
- Rare channelopathy involving α-1 subunit of skeletal muscle Na^+ channel (SCN4A)
- Age of onset: infancy to second decade of life
- May be associated with prolonged QT interval, malignant hyperthermia
- Episodic weakness or paralysis may be precipitated by rest after activity, changes in daily level of activity especially in cool temperatures, K^+ ingestion
- Attacks last 10 to 60 minutes, rarely 1 to 2 days; abrupt paralysis onset may cause falls.
- Stiffness may be aborted with walking, high carbohydrates (candy) ingestion
- *S*$[K^+]$ is most often normal, may be minimally high or even low during recovery
- Diagnosis:
  - Compound muscle amplitude test
  - Genetic testing for a small number of mutations is available.
- Treatment: diet: high carbohydrates, candy; avoid high K^+-containing foods; consider diuretics (thiazides, loop diuretics), β-agonists such as albuterol.

Succinylcholine

Administration of succinylcholine to susceptible patients with conditions where there is upregulation of acetylcholine receptors (eg, neuromuscular disease, severe trauma, burns, chronic immobilization, or infections). Succinylcholine activation of acetylcholine receptors causes cell depolarization and large K^+ efflux.

Antihypertensives

Of interest, a study published in 2017 involving greater than 150,000 participants from the Geisinger Health Care System over 3-year follow-up revealed that the adjusted risks for hyperkalemia (serum K^+ >5.0 mmol/L) associated with the use of antihypertensive agents were 1.54 for angiotensin-converting enzyme inhibitor (ACEI), 1.13 for β-blockers, 1.07 for angiotensin receptor blocker (ARB).

Others

Selective impairment of K^+ secretion/excretion from various mechanisms: tubulointerstitial disease, lupus nephritis, sickle cell disease

Common Clinical Scenarios With Multiple Etiologies/Mechanisms for Hyperkalemia

Patient with diabetes

- Neurogenic bladder leading to urinary stasis
- Low aldosterone state due to reduced sympathetic stimulation for renin release, adrenal atrophy, use of renin-angiotensin-aldosterone inhibitors
- Insulin deficiency leading to reduced cellular K^+ uptake via Na^+-K^+-ATPase
- Hyperosmolality from hyperglycemia leading to cellular K^+ efflux
- Severe metabolic acidosis with DKA leading to K^+ efflux
- Hypovolemia leading to reduced Na^+ delivery to ENaC in collecting tubules, hence reduced K^+ secretion

Patient with cirrhosis or heart failure

- Use of spironolactone
- Low effective circulating volume leading to poor Na^+ delivery to collecting tubules
- Recurrent kidney injuries

Exercise-induced hyperkalemia

- Delayed extracellular shift K^+ during depolarization and subsequent cellular reuptake via Na^+-K^+-ATPase
- Exercise-induced reduction in ATP reduces ATP-dependent inhibition of K^+-channels, hence more open K^+ channels, and increase K^+ leak extracellularly.
- Of note, extracellular K^+ shift is thought to be adaptive since higher K^+ concentration has a vasodilatory effect, hence improved blood flow and energy supply to exercising muscles. Exercise-induced hyperkalemia reverses within a few minutes of rest.

Heparin (both regular and low-molecular weight)

- Inhibition of aldosterone production via reduction in the number and affinity of Ang II receptors in zona glomerulosa
- Inhibition of the final enzymatic step of aldosterone formation (18-hydroxylation)
- Adrenal hemorrhage causing hypoaldosteronism
- K^+ leakage out of white blood cells in heparin-containing test tubes

Hepatitis and cirrhosis

- Use of K^+-sparing diuretics (eg, spironolactone)
- Increased K^+ intake: oral or intravenous supplement, blood transfusions
- Antibiotics (eg, penicillin-K, trimethoprim)

- Cell lysis (rhabdomyolysis, hemolysis)
- Low effective circulating volume
- Concurrent acute kidney injury
- Hyperkalemia associated with the use of sofosbuvir-based regimens in patients with CKD stage 5 and hepatitis C virus infection has been reported. Unclear mechanisms
- Note that although all conditions above predispose patients with liver disorder to hyperkalemia, autoimmune hepatitis is associated with dRTA type 1, where hypokalemia is characteristic.

Post-surgical hyperkalemia may occur following major surgeries, particularly vascular surgeries, due to tissue injury and traumatic hemolysis. Obstructive uropathy should also be considered, for example, clotted Foley or neurogenic bladder with opioids and diphenhydramine use.

Management of Hyperkalemia (Table 2.6)

Table 2.6 Therapeutic options for hyperkalemia

Therapeutic options		Dosing	Onset	Comments
Stabilize cardiac membrane potential.	Calcium gluconate	• 10 mL of 10% of Ca-gluconate infused over 10 min • Note: 1 ampule of $CaCl_2$ = 3 ampules of Ca-gluconate in terms of elemental Ca^{2+}	1-3 min	• $CaCl_2$ can be irritating to vein. • Do not give calcium in HCO_3 line. • Unclear risks/benefits for Ca^{2+} infusion in digoxin-induced hyperkalemia.
Increase cellular uptake.	Insulin PLUS glucose	• 10 units of regular insulin PLUS • Glucose supplement if serum level <250 mg/dL	15-30 min	Reduce insulin dose to 5 units in advanced CKD to reduce hypoglycemia risk.
	Albuterol—β2 agonist	10-20 mg nebulizer	15-30 min	• Risk of tachycardia, precipitation of myocardial infarction • Lactic acidosis type B may occur (see "Lactic acidosis" section).
	$NaHCO_3$	1 mmol/kg	15-30 min	• Do not give in calcium line.

Therapeutic options		Dosing	Onset	Comments
		(if pH <7.2 or advanced CKD)		• Avoid if high $CaxPO_4$ product or volume overload. • **$NaHCO_3$ is not effective in absence of acidemia.**
Increase gastrointestinal (GI) excretion.	Sodium polystyrene sulfonate (SPS)—cation exchanger (Kayexalate)	30-60g oral or per rectum Up to qid + laxative if oral	Variable Hours to days	• Site of action is colon/rectum. • Colonic ischemia and necrosis with and without concurrent use of sorbitol • **Contraindicated in bowel obstruction, ileus, postanesthesia** • Poor efficacy; experts suggest against the use of SPS.
	Patiromer (Veltassa)—Ca^{2+}-K^+ cation exchanger	• 8.4-25.2 g qd • Administer other oral medications >3 h from patiromer and >6 h for those with delayed gastric emptying	7 h	• K^+-binding capacity is ~2 times that of SPS. • Site of action is colon. • May bind Mg^{2+} and NH_4^+ • **May reduce serum Mg^{2+} and increase Ca^{2+}** • May reduce aldosterone level, albuminuria, and blood pressure
	Sodium zirconium cyclosilicate (Lokelma)—Na^+-K^+-cation exchanger	5-10 g qd	**As soon as 1 h**	• K^+-binding capacity is ~9 times that of SPS and 125 times more selective for K^+ than Ca^{2+} or Mg^{2+}. • Binds K^+ throughout GI tract. • Can bind and remove H^+; may benefit acidemia • Can increase gastric pH and affect gastric pH dependent drug absorption

Therapeutic options	Dosing	Onset	Comments
			• Notable side effects: edema, constipation
Increase renal excretion.	• Volume resuscitation if hypovolemia • Loop/thiazide diuretics if hypervolemia • Fludrocortisone if low mineralocorticoid state		
Blood removal	Kidney replacement therapy: HD is preferred over peritoneal dialysis or continuous kidney replacement therapy for faster K^+ clearance.		

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis.

- For patients with relatively good kidney function and nonthreatening electrocardiogram (ECG) changes
  - If hypovolemic, initiate volume resuscitation with normal saline.
  - If hypervolemic, use loop diuretic.
- For serum K^+ greater than 6.5 mmol/L
  - Use insulin/glucose and β2-agonist.
  - Add calcium gluconate if ECG changes or if K^+ is greater than 6.5 mmol/L, even if the ECG remains normal.
- For hyperkalemia with high-risk ECG changes and kidney failure, perform emergent dialysis.
  - Avoid dialysate with K^+ less than 2 mmol/L; may be associated with greater mortality
  - If CKRT is used, initially maximize flow rates to achieve safer K^+ levels.
- For chronic management of hyperkalemia:
  - Remove offending agent.
  - Consider nutrition consult for low-K^+ diet (≤60-75 mmol/d ~ 2,400-3,000 mg/d); avoid salt substitutes, highly processed food (rich in potassium additives).
  - Ensure a good bowel regimen.
  - Consider potassium binding resins: patiromer (Veltassa), sodium zirconium cyclosilicate (Lokelma). See **Table 2.6** for important differences among these agents.

HYPOKALEMIA

Clinical Manifestations

- Muscle weakness, rhabdomyolysis, fatigue, ileus, constipation, leg cramps, respiratory difficulty, HTN

- ECG changes: U waves, T-wave flattening, ST-segment depression, arrhythmias, asystole
- Nephrogenic diabetes insipidus, hypokalemic nephropathy characterized by tubular atrophy and tubulointerstitial fibrosis (**Figure 2.14**), tubulointerstitial and cystic changes

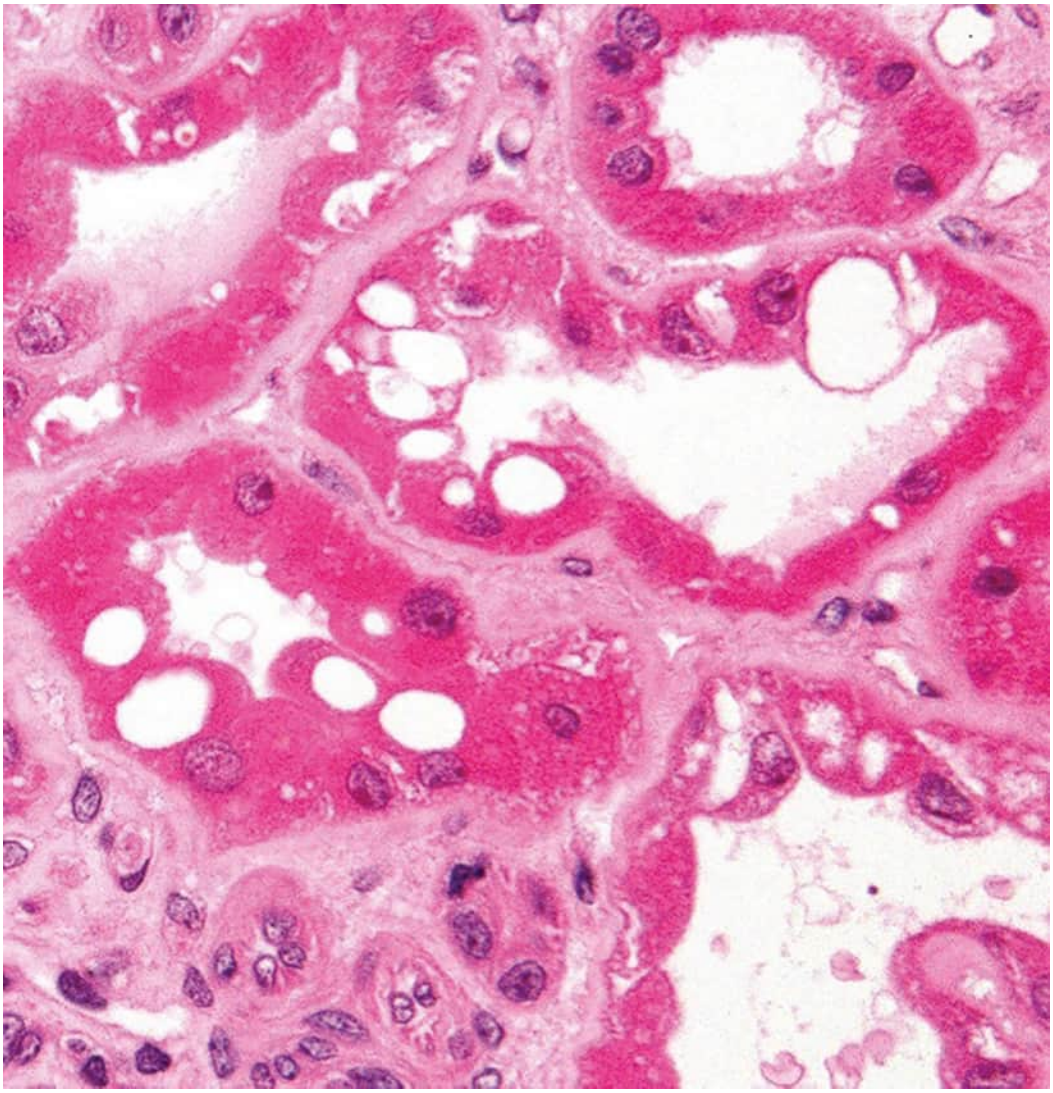


FIGURE 2.14 **Hypokalemic nephropathy.** Tubular epithelial cells containing large irregular cytoplasmic vacuoles and showing acute injury with focal loss of brush border staining and cytoplasmic volume (hematoxylin and eosin stain [H&E] × 60).

- Hypokalemia may be associated with the development of new-onset DM, presumably via reduced pancreatic K^+-dependent insulin release.
- 40% of patients with hypokalemia also have hypomagnesemia. Possible mechanisms include:

- Underlying abnormality/pathology can cause both (eg, cisplatin, amphotericin, diuretics use, poor dietary intake, diarrhea).
- Mg^{2+} is a gatekeeper for ROMK. Low Mg^{2+} leaves ROMK wide open, thus K^+ wasting.
- Mg^{2+} is a cofactor for Na^+-K^+-ATPase and H^+-K^+-ATPase.
- Hypomagnesemia may be associated with an enhanced aldosterone state, where renal K^+ wasting also occurs.

Causes and Mechanisms of Hypokalemia (Figure 2.15)

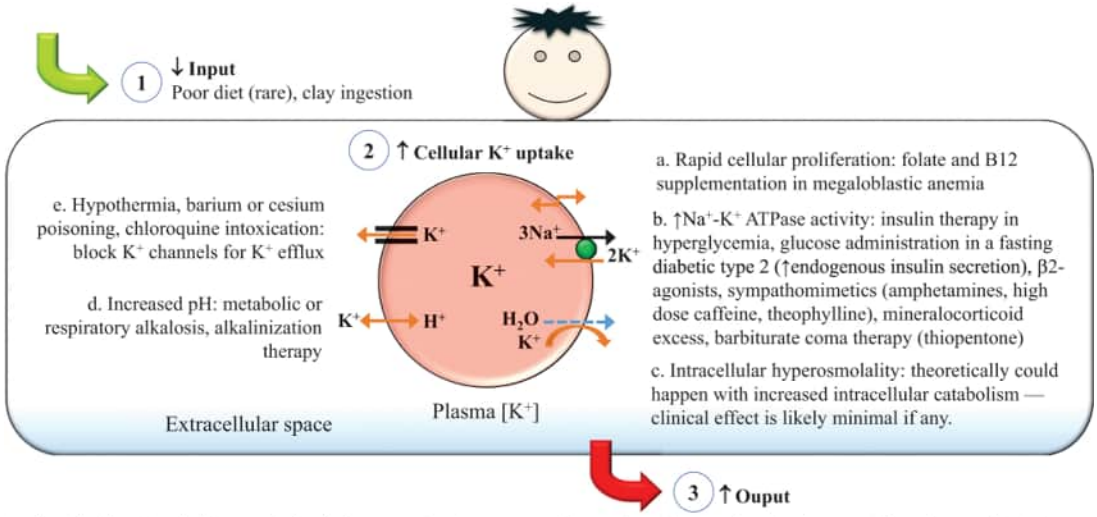

1 ↓ Input
Poor diet (rare), clay ingestion
2 ↑ Cellular K+ uptake
a. Rapid cellular proliferation: folate and B12 supplementation in megaloblastic anemia
b. ↑Na+-K+ ATPase activity: insulin therapy in hyperglycemia, glucose administration in a fasting diabetic type 2 (↑endogenous insulin secretion), β2-agonists, sympathomimetics (amphetamines, high dose caffeine, theophylline), mineralocorticoid excess, barbiturate coma therapy (thiopentone)
c. Intracellular hyperosmolality: theoretically could happen with increased intracellular catabolism — clinical effect is likely minimal if any.
e. Hypothermia, barium or cesium poisoning, chloroquine intoxication: block K+ channels for K+ efflux
d. Increased pH: metabolic or respiratory alkalosis, alkalinization therapy
K+
3Na+
2K+
H+
H2O
Extracellular space
Plasma [K+]
3 ↑ Ouput
Gastrointestinal tract: diarrhea, biliary fluid loss, Ogilvie syndrome, bowel cleansing agents: phenolphthalein laxatives, gut K+-binders
Kidneys: Increased K+ secretion at connecting/collecting tubules: (1) High Na delivery: high fluid intake/infusion, diuretics, Bartter, Gitelman, nonreabsorbable anions (penicillins, bicarbonate, β-hydroxybutyrate, hippurate); (2) Increased ENaC activity: Liddle syndrome; (3) Mineralocorticoid excess (high aldosterone state with acute vomiting); (4) High urine flow: high fluid intake (affecting Big K), diuretics, hypercalcemia, hypomagnesemia;(5) Nonspecific-tubular injuries: Amphotericin B, salt-wasting nephropathies, tubulointerstitial diseases, tubular injuries: cisplatin, aminoglycosides, acute monocytic or myelomonocytic leukemia with lysozyme induced tubular injury leading to K+ wasting

FIGURE 2.15 **Causes of hypokalemia.**

Pseudohypokalemia

- Hypokalemia is present in vitro (test tube) but not in vivo.
- Correction (treatment) of pseudohypokalemia is not necessary.
- Pseudohypokalemia may be seen in patients with acute (or chronic) myeloid leukemia due to continuing cellular K^+ uptake into rapidly proliferating cells even after the blood is drawn. There may be associated pseudohypoglycemia and hypophosphatemia.
- Seasonal pseudohypokalemia due to increased intracellular K^+ uptake via increased Na^+-K^+-ATPase activity with the transport of blood tubes in warm ambient temperatures

Decreased K^+ input

- Severe malnutrition with poor dietary K^+ intake (recommended K^+ dietary is 4,700 mg/d for healthy adults); hypokalemia due to poor intake is rare due to the kidneys' ability to minimize K^+ loss to 5 to 20 mmol/L of urine.
- Clay ingestion "geophagia." Clay can bind K^+ in the intestines.

Increased Bodily K^+ Loss/Output

GI loss

Vomiting: Hypokalemia associated with vomiting predominantly occurs via renal K^+ loss due to volume depletion–induced hyperrenin, hyperaldosteronism, and bicarbonaturia. Gastric fluid [K^+] only contains 10 to 15 mmol/L.

Diarrhea [K^+] typically ranges from 10 to 40 mmol/L but can exceed 100 mmol/L in colonic fluid in Ogilvie syndrome.

Ogilvie syndrome

- Acute colonic pseudo-obstruction (dilated colon) associated with secretory diarrhea with very high K^+ content due to activation of colonic K^+ secretion
- This condition is seen in the older patient and is associated with acute illnesses/stressors.
- Associated electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
- Treatment: electrolyte replacement

Bowel cleansing agents: phenolphthalein laxatives, potassium binders (see **Table 2.6**)

Increased renal K^+ excretion

- Recall renal K^+ secretion depends on (1) distal Na^+ delivery, (2) generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in principal cells at ASDN segment, (3) distal urine flow, (4) presence of aldosterone (mineralocorticoid), (5) sensitivity to aldosterone (mineralocorticoid), (6) kidney mass/function.
- Enhanced renal K^+ secretion occurs with overactivity of any of factors 1 to 6 listedearlier. Study **Table 2.7**. Also, see "Selected Renal Causes of Hypokalemia" section.

Table 2.7 Renal causes of hypokalemia

Factors involved in normal renal K^+ secretion	Corresponding problems that may lead to renal K^+ secretion	Comments
Na^+ delivery to distal segment (connecting/ collecting duct [CN/CD])	Increased Na^+ delivery: • Diuretics, high intravenous fluid infusion • Bartter and Gitelman syndromes	Recall increased tubular flow also activates BK channel which increases K^+ loss.
Increased ENaC activity	Gain-of-function mutation of ENaC: Liddle syndrome	• Autosomal dominant, gain-of-function mutation of ENaC • Clinical manifestations: HTN, hypokalemia, metabolic alkalosis; hyporenin, hypoaldosterone; treatment: ENaC inhibitor, e.g., amiloride
Generation of negative lumen following Na^+ entry via ENaC	Nonreabsorbable anions: eg, bicarbonate (vomiting and proximal renal tubular acidosis), β-hydroxybutyrate (diabetic ketoacidosis), high-dose penicillin/penicillin derivative, hippurate (toluene with glue sniffing)	• Delivery of Na^+ associated with nonreabsorbable anions to ENaC increases K^+ and H^+ secretion at CN/CD causing hypokalemia and metabolic alkalosis, respectively. • The nonreabsorbable anions also contribute to the negative lumen potential that favors the secretion of both K^+ and H^+ into the lumen.
Aldosterone or any molecule with mineralocorticoid activity (Mineralocorticoid upregulates ENaC, ROMK, Na-K-ATPase activities, thereby increasing renal K^+ secretion.)	Hyperaldosteronism: hyperfunctioning adrenals, glucocorticoid remediable aldosteronism	• Remove offending agents. • For primary adrenal insufficiency: Treat with hydrocortisone ± fludrocortisone.
	Hypercortisolism: Cushing disease/syndrome, licorice ingestion, syndrome of apparent mineralocorticoid excess	• Cortisol has mineralocorticoid activity.
	Deoxycorticosteroid excess • Congenital adrenal hyperplasia with inactivating mutations of 11-α hydroxylase or 17-β hydroxylase • Deoxycorticosterone-producing tumors • Drug-induced: abiraterone acetate • Chrousos syndrome	• Deoxycorticosterone has mineralocorticoid activity. • See text for explanations on how congenital adrenal hyperplasia, abiraterone acetate, and Chrousos syndrome can cause increased deoxycorticosteroid levels.

Factors involved in normal renal K^+ secretion	Corresponding problems that may lead to renal K^+ secretion	Comments
Mineralocorticoid receptor (MR)	Activating mutation of MR, aka Geller syndrome:	• Autosomal dominant disorder where MR is constitutively activated. • Progesterone and its derivatives may activate transcription of the mutated MR. Pregnancy-induced HTN and hypokalemia may develop. • Spironolactone may stabilize the mutated active MR and worsen HTN. • Treatment: nonspecific treatment of HTN and hypokalemia during pregnancy
Good urine flow	High volume intake/infusion, diuretics	Recall increased tubular flow also activates BK channel which increases K^+ loss.
Kidney mass/function	Glomerular hyperfiltration	

Abbreviations: BK, Big-K; ENaC, epithelial sodium channel; HTN, hypertension; ROMK, renal outer medullary potassium channel.

Miscellaneous sources of bodily K^+ loss

- Excessive sweats, extensive burns
- Dialysis, plasmapheresis

Selected Renal Causes of Hypokalemia

Liddle syndrome

- Autosomal dominant gain-of-function mutation in the β- and γ-subunits of ENaC that reduces the "housekeeping" recognition of ENaC by the enzyme Nedd4-2 for internalization and degradation, resulting in an increased number of functioning apical ENaC.
- Affected patients present with HTN due to excess Na^+ retention, hyporenin and hypoaldosteronism due to volume expansion, and hypokalemia and metabolic alkalosis due to facilitated renal K^+ and H^+ secretion, respectively, following increased Na^+ entry into the nondegraded apical ENaC. Typical age of onset is 15 years old but may occur in adulthood.

- Treatment: dietary sodium restriction and direct ENaC inhibitors such as amiloride and triamterene. Spironolactone is *ineffective* since Liddle syndrome is not due to aldosterone-induced upregulation of ENaC. Liddle syndrome is curable with kidney transplantation.

Nonreabsorbable anions (eg, Na^+ – [nonreabsorbable] $anion^-$)

- Delivery of Na^+ (associated with its nonreabsorbable anion) to ENaC enhances K^+ and H^+ secretion at CN/CD, causing hypokalemia and metabolic alkalosis, respectively.
- The nonreabsorbable anions also contribute to the negative lumen potential that serves to facilitate K^+ and H^+ secretion.
- Examples of nonreabsorbable anions: bicarbonate (vomiting and pRTA), β-OH in DKA, high-dose penicillin/penicillin derivative administration, hippurate from toluene with glue sniffing

Increased mineralocorticoid activity and mimickers (Figure 2.16)

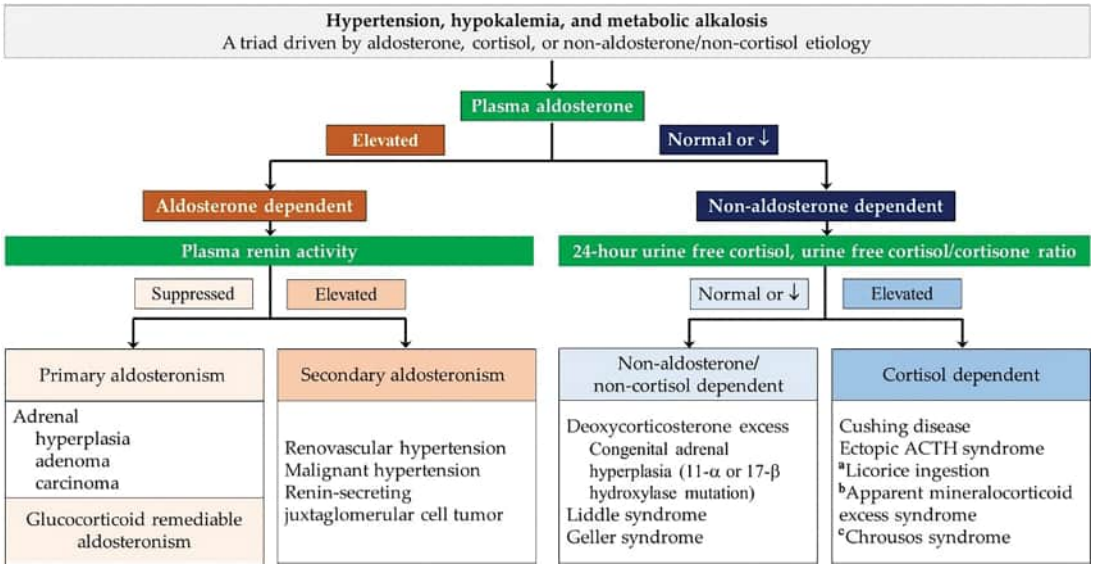


FIGURE 2.16 Evaluation of conditions associated with the triad of hypertension, hypokalemia, and metabolic alkalosis.

Abbreviation: ACTH, adrenocorticotropin hormone.

[a]Glycyrrhizic acid and its hydrolytic product glycyrrhetinic acid from licorice are potent competitive inhibitors of 11-β hydroxysteroid dehydrogenases, the enzyme required to metabolize cortisol to its inactive form, cortisone.[b] Apparent mineralocorticoid excess: mutation of 11-β hydroxysteroid dehydrogenase enzyme.[c] Deoxycorticosterone excess: adrenal hyperplasia (mutations involving 11-α hydroxylase or 17-β hydroxylase), Chrousos syndrome (inactivating glucocorticoid receptor gene mutation).

- The clinical triad of HTN, hypokalemia, and metabolic alkalosis may be categorized as aldosterone dependent, cortisol dependent, or non-aldosterone and non-cortisol dependent.

Aldosterone-dependent conditions

- Primary aldosteronism: Aldosterone synthesis is independent of renin (eg, adrenal hyperplasia, adenoma, or carcinoma, glucocorticoid-remediable aldosteronism [GRA]).
- GRA:
  - Autosomal dominant condition where there is formation of a chimeric gene resulting from the unequal crossover of sequences at meiosis. This hybrid gene places the promoter of 11-β hydroxylase enzyme (enzyme for cortisol synthesis) upstream to aldosterone synthase gene (enzyme for aldosterone synthesis).
  - Adrenocorticotropin hormone (ACTH) stimulation of the promoter for the 11-β hydroxylase enzyme upregulates both cortisol and aldosterone synthesis.
  - Clinical manifestations: early moderate to severe HTN, hemorrhagic stroke and ruptured aneurysms (brain magnetic resonance angiography [MRA] every 5 years after puberty has been recommended), normo- to hypokalemia (the former due to the diurnal variation of ACTH)
  - Diagnosis:
    - Genetic testing
    - Biochemical evaluation: low renin, high serum aldosterone, increased levels of 18-hydroxy-cortisol, ACTH, and 18-oxo-cortisol
  - Treatment:
    - Direct therapy: glucocorticoid (to suppress ACTH)
    - Alternative therapy: MR antagonists (spironolactone, eplerenone, finerenone) ± ENaC antagonism (amiloride)
- Secondary aldosteronism:
  - High renin level stimulates aldosterone synthesis.
  - Source of renin: hypoxia-induced (renovascular HTN) or unregulated synthesis (renin-secreting tumors, ie, juxtaglomerular cell tumors)

Cortisol dependent

- Excess production of cortisol (Cushing syndrome and ectopic ACTH release)
- Reduced inactivation of cortisol to cortisone by 11-β hydroxysteroid dehydrogenase type 2 (11-βHSD2)
  - Licorice: glycyrrhizic acid and its hydrolytic product, glycyrrhetinic acid, from licorice are potent competitive inhibitors of 11-βHSD2.

- Mutation of 11-βHSD2: syndrome of apparent mineralocorticoid excess (SAME)
- Diagnosis of excess cortisol:
  - Both urinary free cortisol and cortisone are high in conditions with excess cortisol production (eg, Cushing disease or syndrome).
  - A cortisol-to-cortisone ratio of greater than 1 is consistent with reduced 11-βHSD2 activity, for example, licorice ingestion (assuming normal urinary cortisone excretion). Normal cortisol-to-cortisone ratio is less than 0.5.
  - A cortisol-to-cortisone ratio of greater than 5 is consistent with SAME.

Non-aldosterone and non-cortisol dependent

- Liddle syndrome (see earlier) mimicking excess mineralocorticoid state
- Deoxycorticosteroid (DOC) excess:
  - DOC has mineralocorticoid activity.
  - Conditions associated with DOC excess
    - Congenital adrenal hyperplasia (CAH) involving inactivating mutations of 11-α hydroxylase leads to defective cortisol synthesis and the resultant increase in desoxycortisol and desoxycorticosterone, which have mineralocorticoid activity.
    - Inactivating mutation of 17-β hydroxylase leads to defective cortisol, androgen, and estrogen synthesis and the resultant increase in the synthesis of deoxycorticosterone and varying levels of aldosterone. In mutations involving 11-α and 17-β hydroxylase, cortisol level is low.
    - Deoxycorticosterone-producing adrenal tumors
    - Abiraterone acetate-induced DOC excess: Abiraterone is an inhibitor of androgen synthesis used to treat metastatic or castration-resistant prostate carcinoma or androgen receptor-positive breast carcinoma. Abiraterone inhibits 17-α hydroxylase which reduces downstream cortisol synthesis. Hypocortisolism activates ACTH which drives upstream synthesis of DOC. DOC has mineralocorticoid activity that can lead to sodium retention, hypokalemia, and HTN. This abiraterone-induced complication can be treated with eplerenone up to 200 mg/d or low-dose dexamethasone (0.5 mg/d).

Activating mutation of MR, aka Geller syndrome

- Autosomal dominant disorder where the conformation of MR is altered and constitutively activated
- During pregnancy, progesterone and its derivatives may activate transcription of the mutated MR, leading to pregnancy-induced HTN and hypokalemia. Renin and aldosterone levels are typically low.

- Spironolactone (normally an MR antagonist) may stabilize the mutated MR in its active conformation thereby worsening HTN. Treatment involves nonspecific HTN management and potassium supplements as needed. This condition typically resolves postpartum.

Miscellaneous Causes of Hypokalemia

Chrousos syndrome is caused by an inactivating glucocorticoid receptor gene mutation causing resistance of tissues to glucocorticoids. Subsequent increase in corticotropin secretion results in hypersecretion of cortisol, corticosterone, and DOC and resultant HTN and hypokalemic alkalosis.

Amphotericin B is a multiplanar molecule that is lipophilic on the outside and hydrophilic on the inside surface. The molecule inserts itself into the tubular cell membrane and acts as an ionophore allowing electrolytes to flow in the direction of a favorable chemical gradient. The formulation of liposomal amphotericin covers up the lipophilic surface of amphotericin and limits its insertion into tubular membranes, thus minimizing intracellular electrolyte losses into the urinary space and back-leak of H^+ into circulation (see **Figure 2.7**).

Magnesium deficiency can lead to K^+ wasting at the TAL. Mg^{2+} is a "gatekeeper" against K^+ secretion via ROMK.

Hypercalcemia (inhibits ROMK in TAL and induces a form of nephrogenic diabetes insipidus)

Others: salt-wasting nephropathies, tubular injuries (tubulointerstitial diseases, cisplatin, aminoglycosides), acute monocytic or myelomonocytic leukemia with lysozyme-induced tubular injury leading to K^+ wasting

Intracellular K^+ Shift

Increased extracellular pH

In metabolic and respiratory alkalosis, net intracellular K^+ uptake may be observed. The effect of K^+ shifting is less pronounced in respiratory compared to metabolic processes.

Increased Na^+-K^+-ATPase activity

- Insulin administration or endogenous insulin release with glucose administration (eg, dextrose 5% saline solution)
- NOTE: in patients with diabetes with poorly controlled glucose and preexisting life-threatening hypokalemia, provide K^+ replacement *prior* to insulin administration to avoid further fall in preexisting low $S[K^+]$.
- Increased β-2 adrenergic activity increases cellular K^+ uptake: stress, coronary ischemia, delirium tremens, thyroid hormone, β2-agonists (albuterol,

terbutaline, dopamine, dobutamine, pseudoephedrine), sympathomimetic stimulants (eg, amphetamines, high-dose caffeine), theophylline toxicity

Inhibition of ATP-sensitive K^+ channels blocks K^+ efflux during repolarization: hypothermia, barium/cesium poisoning, chloroquine intoxication

Hypokalemic periodic paralysis

- Rare channelopathy (autosomal dominant, varying penetrance)
- 90% with mutation of the α-1 subunit of dihydropyridine (DHP)-sensitive Ca^{2+} channel (CACNA1S), 10% with mutation of the SCN4A, that can lead to K^+ efflux.
- **Clinical manifestations:**
  - Attacks often begin in adolescence.
  - Muscle weakness or paralysis in association with a fall in $S[K^+]$: affects upper extremities more than lower extremities; shows proximal more than distal weakness
  - May be associated with hypophosphatemia and hypomagnesemia
  - Triggered by strenuous exercise followed by rest, high-carbohydrate high-sodium meals or administration of glucose, insulin, or glucocorticoids, sudden changes in temperature, excitement, loud noise, or flashlights
- **Associated conditions**
  - Andersen syndrome associated with prolonged QT and sudden death
  - Thyrotoxicosis due to Graves disease: more common in Asian or Latin/Native American males (propranolol may reverse attacks pending definitive therapy). Of note, patients with thyrotoxicosis hypokalemia periodic paralysis may also have elevated bone alkaline phosphatase for unclear reasons.
- **Diagnosis:** electromyograms during attacks or with exercise
- **Treatment:**
  - Potassium supplement (slow and low dose due to rebound hyperkalemia)
    - If the patient can swallow and breathe adequately, provide oral KCl, K-citrate, or K-bicarbonate 20 mmol q2h intervals, maximum 90 mmol/24 h. Monitor $S[K^+]$ closely.
    - If cannot swallow: KCl 15 mmol over 15 minutes then 10 mmol/h in 500 mL dilutant; 5% mannitol dilutant is preferred over normal saline (sodium may worsen the condition). DO NOT use glucose (due to endogenous insulin secretion and exacerbation of hypokalemia).
  - Cardiac monitoring is required with intravenous KCl administration.

- Prevention: β2-blockers, K^+ supplement, low-carbohydrate diet, K^+-sparing diuretics, CA inhibitor (acetazolamide)
- Treat thyroid disease if applicable.

Barbiturate coma therapy (BCT)

- BCT is the choice therapy for refractory intracranial HTN to reduce cerebral blood flow, metabolic rate of oxygen consumption, and intracranial pressure (ICP).

Thiopentone is a BCT that can commonly induce dyskalemias.

- Initial hypokalemia:
  - Hypokalemia has been reported in 65% to 89%.
  - Severe hypokalemia (<2.0 mmol/L) has been reported in 25% of patients.
  - Refractory life-threatening hypokalemia may occur.
  - Median onset of hypokalemia is 11 hours (6-23 hours) with nadir at 25 hours after BCT induction.
- Rebound hyperkalemia (may be severe) following BCT cessation:
  - Peak $S[K^+]$ exceeding 6 mmol/L may occur at mean 31 hours (28-56 hours).
  - Abrupt BCT cessation leading to $S[K^+]$ increase within 2 hours has been reported.
- Management:
  - Hypokalemia during BCT:
    - Avoid overly aggressive K^+ replacement.
    - Maintain $S[K^+]$ goal at 3 mmol/L with cardiac monitoring.
    - Keep total K^+ supplement to less than 100 mmol has been suggested.
  - Slow taper of BCT over 12 to 24 hours has been suggested to reduce rapid and severe rebound hyperkalemia.
  - Monitor $S[K^+]$ and treat as needed over 72 hours following BCT discontinuation.

FYI

Mechanisms of thiopentone-induced dyskalemia are not clear but thought to involve:

- Inhibition of neuronal voltage-dependent outward potassium current
- Inhibition of phosphofructokinase causes a reduction in pyruvate and lactate production. The resultant increase in intracellular pH promotes intracellular K^+ shift.
- Increase β2-stimulation of Na^+-K^+-ATPase activity:
  - The increased ICP may inherently induce a surge of endogenous catecholamine release and β2-stimulation of Na^+-K^+-ATPase pump.

- BCT may stimulate Na^+-K^+-ATPase activity.

Management of Hypokalemia

- If *S*[K+] is less than 3 mmol/L, order a STAT ECG, and start cardiac monitoring.
- If safe, AVOID the following until *life-threatening* hypokalemia has been corrected:
  - The use of glucose-containing solutions, for example, 5% dextrose solutions because of glucose-induced endogenous insulin secretion
  - Correction of hyperglycemia with insulin administration in patients with hyperglycemia
  - Alkalinization
  - Use of β2-agonists
- Use central lines if greater than 10 mmol/h replacement is needed.
- Consider femoral line over the internal jugular or subclavian line if greater than 20 mmol/h replacement is needed to avoid cardiac irritation.
- Check magnesium levels and replace as necessary.

Diagnosis of Potassium Disorders

Common indices used to determine renal versus extrarenal causes of potassium disorders are listed in **Table 2.8**.

Table 2.8 Urinary indices used in the evaluation of potassium disorders

Urinary indices	Hyperkalemia		Hypokalemia	
	[a]Renal cause	Extrarenal cause	Renal cause	Extrarenal cause
Spot $[K^+]$ (mmol/L)	<15	>40	>40	<15
[b]Spot $[K^+]$/[Cr] (mmol/g Cr)	<15	>25	>25	<15
[c]24-h urine K^+ (mmol/d)	<25	>40	>40	<25

Notations: $[K^+]$, urine potassium concentration; [Cr], urine creatinine concentration.

[a]Ranges given are not absolute. Clinical judgment is required.

[b]Spot $[K^+]$/[Cr], spot urine K^+ concentration divided by urine creatinine concentration. Spot urine studies are fast and easy to obtain. Spot urine $[K^+]$/[Cr] ratio is expected to provide a better assessment of renal K^+ excretion compared with spot $[K^+]$.

[c]24-hour urine K^+ is the gold standard but the most difficult and cumbersome to obtain.

Bartter versus Gitelman Syndrome (BS versus GS)

Traditionally, BS and GS are likened to taking loop and thiazide diuretics, respectively. As such, these syndromes are associated with salt loss, polyuria, normo- or hypotension, and "compensatory" activation of the RAAS without concurrent HTN. Similar to diuretics, both BS and GS are associated with hypokalemia and metabolic alkalosis.

In BS, increased synthesis of the vasodilatory prostaglandin E2 (PGE2) also contributes to the normotensive state despite having stimulated RAAS. Impaired chloride reabsorption via NKCC2 at macula densa (these are specialized thick ascending loop of Henle cells) is sensed as having low chloride delivery. This leads to increased PGE2 synthesis and subsequent RAAS activation. The use of nonsteroidal anti-inflammatory drugs (NSAIDs; indomethacin) can improve symptoms and electrolyte disturbances in patients with BS and hyperprostaglandin E syndrome.

Common Findings of BS and GS

- Triad: normotension, hypokalemia, and metabolic alkalosis
- Elevated plasma renin activity and aldosterone level
- NOTE: These clinical findings may also be found in diuretic abuse, surreptitious vomiting/bulimia, and chloridorrhea. Urine chloride levels can be variable with intermittent diuretic misuse and surreptitious vomiting, low in chloridorrhea and associated volume depletion, and persistently elevated in BS and GS.

Differences Between BS and GS

- Age of onset is typically ante- and neonatal with BS and early infancy/adulthood in GS.
- Hypercalciuria is common in BS while hypocalciuria is common in GS.
- Severe hypomagnesemia is more common in GS.
- Exceptions to all the above have been reported.
- Disctinction between BS and GS:
  - Genetic analysis
  - Response to thiazide: NaCl excretion is increased in patients with BS but not GS.

Bartter syndrome

- Clinical manifestations common to BS:

- Commonly occurs in the antenatal or neonatal period except BS type 5 which may present in late childhood or early adulthood
- Intrauterine growth restriction, polyhydramnios, failure to thrive
- Nephrocalcinosis (less common in BS types 3 and 4)
- Laboratory findings in addition to hypokalemia and metabolic alkalosis: hypercalciuria, high urine PGE2 level, ± hypomagnesemia
- Reduced concentrating and diluting capacity because the ascending loop of Henle is affected.
- Secondary focal segmental glomerulosclerosis, presumably adaptive to stimulated RAAS, has been reported in patients with BS.

FYI

K^+ recycling back into the lumen via ROMK creates a positively charged lumen. The positively charged lumen facilitates divalent cation (Ca^{2+}, Mg^{2+}) reabsorption paracellularly, a process facilitated by the tight junction proteins claudin 16 (aka paracellin 1) and 19. Any transporter defect leading to suboptimal K^+ recycling or mutation of claudin 16/19 can induce Ca^{2+} and Mg^{2+} wasting. Urinary calcium wasting explains nephrocalcinosis commonly observed among BS.

- The different types of BS are depicted in **Figure 2.17**.

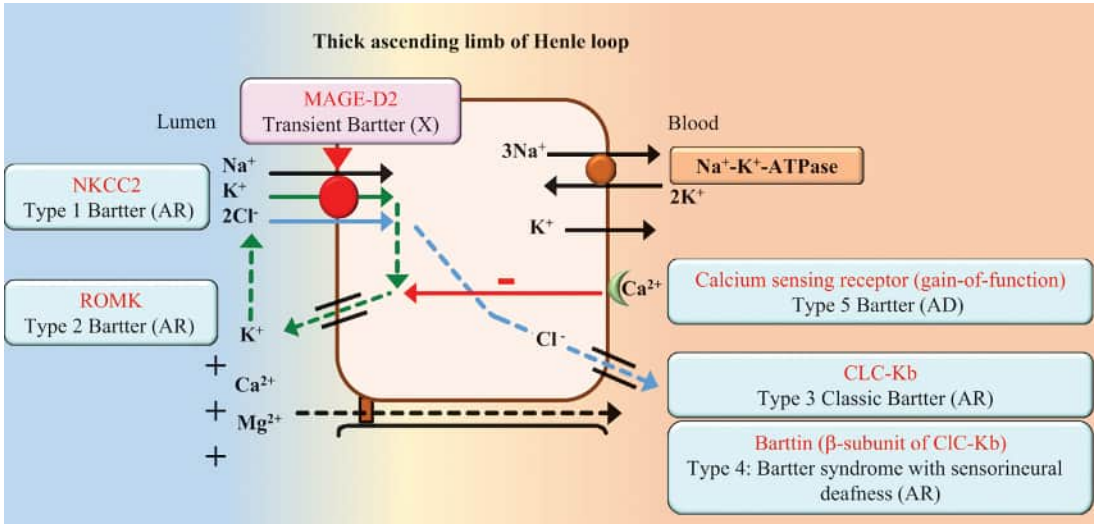


FIGURE 2.17 Mutations associated with Bartter syndrome.
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ClC, chloride channel; MAGE-D2, melanoma-associated antigen D2; NKCC2, sodium-potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel.

Type 1 involves mutation of NKCC2.
Type 2 involves mutation of ROMK.
Type 3 aka Classic Bartter syndrome

- Typically presents in infancy/early childhood

- Mutation of chloride channel Kb (ClC-Kb)
- Patients with BS 3 typically present with more severe chloride depletion because ClC-Kb is present in both TAL and distal nephron (DCT).
- Urinary Ca^{2+} level is variable because although dysfunctional ClC-Kb at NKCC2 induces calciuria, its presence in DCT can reduce Na^{+} reabsorption at NCC and effectively functions as a mild thiazide diuretic, thereby increasing Ca^{2+} reabsorption.

Type 4a: BS and sensorineural deafness (BSND)

- Mutation of barttin subunit of the chloride channel ClC. Barttin subunit is required in both ClC-Ka and ClC-Kb for normal function.

Type 4b: BSND, concurrent mutation of ClC-Ka and ClC-Kb

- Patients with BS 4a or 4b typically present with severe phenotypes including growth retardation, poor response to NSAIDs, and even early ESKD.

FYI

- ClC-Ka and ClC-Kb are present in distinct parts of the ascending loop of Henle.
  - ClC-Ka is present in the thin ascending limb of Henle and provides passive transepithelial chloride reabsorption.
  - ClC-Kb is present in the TAL, DCT, and CCD intercalated cells. ClC-Kb is necessary for optimal NKCC2 activity in the outer medullary and cortical TAL. Loss of ClC-Kb function leads to suboptimal NKCC2 activity.
- Both ClC-Ka and ClC-Kb are expressed in the marginal cells of the stria vascularis in the inner ear and contribute to K^{+} secretion into the endolymph necessary for sensory transduction in inner ear hair cells. Simultaneous loss of function of both ClC-Ka and ClC-Kb but not ClC-Kb alone leads to sensorineural deafness.

Type 5

- Gain-of-function mutation of calcium-sensing receptor (CaSR)
- Activation of CaSR reduces intracellular cyclic adenosine monophosphate (cAMP) production and subsequently increases the production of 20-hydroxyeicosatetraenoic acid. The latter inhibits ROMK, thereby inhibiting NKCC2.
- This condition is associated with salt wasting, hypercalciuria, hypocalcemia, and hypomagnesemia.

Transient antenatal BS: loss-of-function mutations of melanoma-associated antigen D2 (MAGE-D2). MAGE-D2 normally interacts with NKCC2 to increase their cell-surface expression and activity. Mutations in MAGE-D2 reduce NKCC2 expression in TAL and NCC in DCT. This form of BS is X-linked and transient in nature.

Drug-induced Bartter-like syndrome (aminoglycosides, calcimimetics, amphotericin B, heavy metal intoxication): Gentamicin can bind and activate basolateral CaSR in TAL to induce a Bartter-like syndrome. The Bartter-like effect may last up to 2 to 6 weeks following drug cessation.

Gitelman syndrome (Figure 2.18)

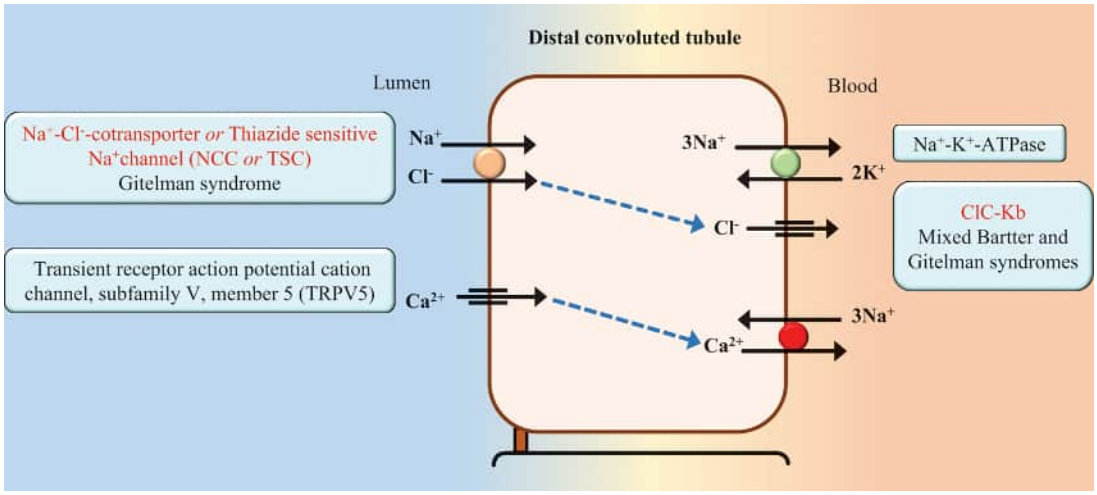


FIGURE 2.18 Mutation of the sodium chloride cotransporter in Gitelman syndrome.
Abbreviation: ClC, chloride channel.

Mutations associated with GS

- Loss-of-function mutation of NCC is responsible for GS.
- Note that ClC-Kb is also present in DCT. This may partly explain mixed BS and GS phenotypes and lack of hypercalciuria with ClC-Kb mutation.

Drug induced: Cisplatin may cause a Gitelman-like syndrome. Pathogenesis is unknown but thought to be due to cisplatin-induced NCC gene injury and DCT apoptosis.

Clinical manifestations of GS

- May present in early childhood or adulthood
- Symptoms are associated with volume depletion and electrolyte disturbances: dizziness, salt craving, polyuria possibly due to chronic hypokalemia-induced nephrogenic diabetes insipidus, hypotension, neuromuscular irritability, weakness, cramps
- HTN may present later in life in some patients with GS, presumably due to chronic RAAS activation without the countereffect of PGE2 seen in patients with BS.
- Hypocalciuria and chondrocalcinosis: Reduced Na^+ reabsorption stimulates basolateral Na^+-Ca^{2+} exchanger activity thereby increasing Ca^{2+} reabsorption

and risk for systemic chondrocalcinosis.

Laboratory findings in addition to hypokalemia and metabolic alkalosis:

- Hypomagnesemia is present in 100% of patients (may be absent in the early phase).
- Hypocalciuria
- Normal urinary PGE2 level

> **FYI**
>
> **Of interest:** Unlike BS, hypomagnesemia is present in almost all patients with GS and is often severe. Reasons are not clear but are suggested below:
>
> - There are apoptotic and/or histologic changes in DCT in patients with GS that could affect DCT Mg^{2+} reabsorption, but not in patients with BS.
> - There is compensatory DCT Mg^{2+} reabsorption with Mg^{2+} wasting from the loop of Henle in BS.

Diagnosis of BS and GS

Suggested laboratory studies to obtain

- Blood gas and routine chemistry, serum magnesium
- Confirm the presence of hypokalemia and metabolic alkalosis.
- Severe hypomagnesemia is more common and severe in GS than in BS.
- Urine studies:
  - Urine osmolality: Isosthenuric or hyposthenuric urine (ie, urine osmolality is ≤serum osmolality) is typically present in patients with BS but may be normally concentrated per volume status in those with GS.
  - Urine chloride is persistently elevated (fractional chloride excretion >0.5%) due to continuing salt wasting.
  - Urine calcium to urine creatinine ratio: Low ratios suggest GS whereas high ratios suggest BS. A ratio of less than 44 mg/g Cr is typical for GS and greater than 200 mg/g Cr for BS.

Genetic testing

Management of BS and GS

- Consider K-sparing diuretics such as amiloride, spironolactone.
- Amiloride (5-20 mg/d) may be used in GS to reduce renal Mg^{2+} and K^{+} wasting.
- NSAIDs or cyclooxygenase COX-2 inhibitors may be considered in poorly controlled BS with hyperprostaglandin syndrome if good kidney function.

- Potassium (K-citrate or modified Shohl solution) and magnesium supplement as needed
- Ad libitum salt intake in individuals with evidence of low salt intake

Metabolic complications with urinary diversions (Table 2.9)

Table 2.9 Metabolic disturbances with urinary diversions

Bowel segment used (procedures)	Acid-base disturbances	Electrolyte disturbances	Comments
Gastric segment (patch for bladder augmentation)	**Metabolic alkalosis**	Hyponatremia, hypokalemia	• Metabolic alkalosis is thought to be due to increased gastrin secretion from the gastric patch which stimulates gastric HCl secretion and urinary acid excretion.
Jejunum (ureterojejunostomy)	Metabolic acidosis	Hyponatremia, **hyperkalemia**	• Hyperkalemia is thought to be due to increased K^+ absorption by jejunum. • The jejunum also avidly absorbs free water and potentially contributes to hyponatremia.
Ileal and colonic segments (ileal conduit, ureterosigmoid anastomosis)	Metabolic acidosis	Hypokalemia	• When ileal and colonic segments are exposed to urine, HCO_3^- is secreted in exchange for Cl^- absorption by the gut mucosa. • Urinary urea is metabolized to HCO_3^- and NH_4^+ by intestinal bacteria. While HCO_3^- is excreted into the stool, NH_4^+ is absorbed by colonic mucosa and transported to the liver via portal circulation where it undergoes metabolism into urea + H^+.

In general, the longer the intestinal segment used and the longer the contact time between urine and intestinal segment, the worse the metabolic complications. Metabolic acidosis is typically worse for ureterosigmoid anastomosis than ileal conduit due to greater contact time between the urine and the longer segment involved with the former procedure. Important differences are bolded.

- In general, the longer the intestinal segment used and the greater the contact time between urine and intestinal segment, the worse the metabolic complications. Metabolic acidosis is typically worse for ureterosigmoid anastomosis than ileal conduit due to greater contact time between the urine and the longer segment involved with the former procedure.

- As urine contact time is typically short with ileal conduit due to rapid drainage into an external collection bag, metabolic acidosis should not occur. If severe metabolic acidosis develops in patients with an ileal conduit, a loopogram should be considered to rule out obstruction.

Gastric Segment

- May be used as a patch for bladder augmentation
- Hypokalemia and metabolic alkalosis may occur.
- Metabolic alkalosis is thought to be due to increased gastrin secretion from the gastric patch which stimulates gastric HCl secretion and urinary acid excretion.

Jejunum Segment

- May be used for ureterojejunostomy
- Hyperkalemia and metabolic acidosis may occur.
- Hyperkalemia is thought to be due to increased K^+ absorption by jejunum.
- Jejunum segment also avidly absorbs electrolyte-free water, which can potentially contribute to hyponatremia in patients with high free water intake.

Ileum and Colon Segments

- May be used as an ileal conduit, ureterosigmoid anastomosis
- Hypokalemia and metabolic acidosis may occur.
- Metabolic acidosis:
  - When ileal and colonic segments are exposed to urine, HCO_3^- is secreted in exchange for Cl^- absorption by the gut mucosa.
  - Urinary urea is metabolized to NH_4^+ and HCO_3^- by intestinal bacteria. While HCO_3^- is excreted into the stool, NH_4^+ is absorbed by colonic mucosa and transported to the liver via portal circulation where they undergo metabolism into urea plus H^+.

CHAPTER 3

Calcium, Phosphorus, and Magnesium Disorders, and Kidney Stones

Phuong-Chi T. Pham, Phuong-Truc T. Pham, Monica Deshmukh, and Phuong-Thu T. Pham

DISORDERS OF CALCIUM METABOLISM

Background

- Calcium is mostly bound and associated with bones (~99% of total body calcium, ~1 kg).
- Extracellular calcium concentration range: 9.0 to 10.6 mg/dL
  - About 40% is protein-bound (mostly albumin). Corrected total serum calcium concentration (SCa) for patients with hypoalbuminemia may be estimated as:

    = Measured SCa + 0.8 × (4.0 − serum albumin concentration)
- About 60% is ultrafilterable.
  - About 40% to 50% exists as free ionized calcium (iCa^{2+}).
  - About 10% is complexed to anions (eg, bicarbonate, citrate, phosphate).
- Intracellular calcium concentration is minute at approximately 100 nmol/L, but it may increase up to 10- to 100-fold during various cellular functions.
- Physiologic roles of calcium: skeletal composition, neuromuscular excitation, cardiac and muscle contractility/function

Calcium Metabolism

Gastrointestinal (GI) tract (Figure 3.1)

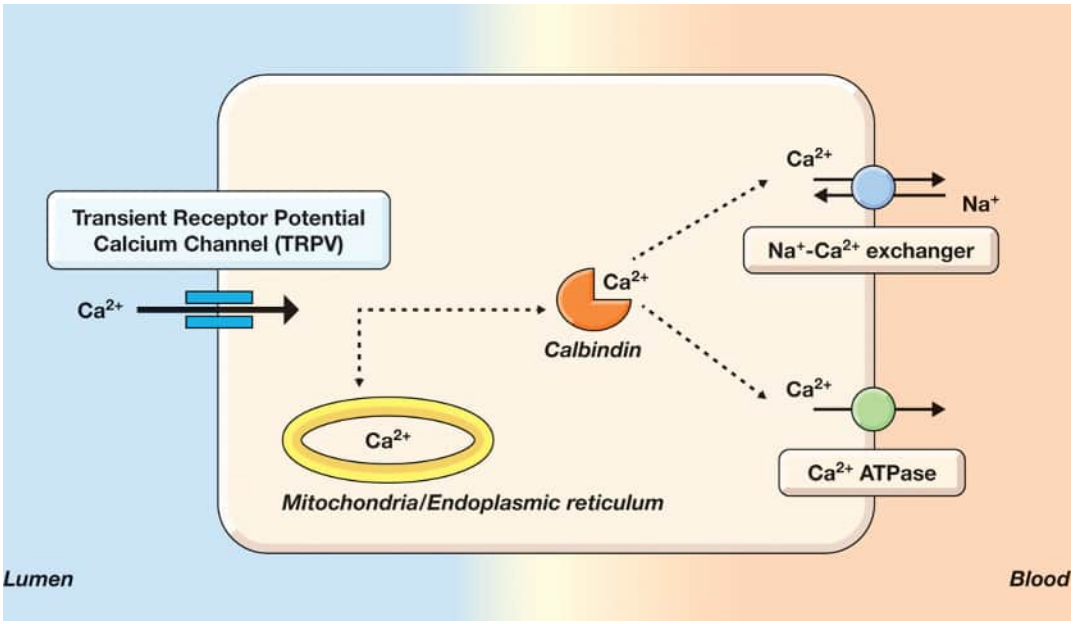


FIGURE 3.1 Epithelial calcium transport is similar in both enterocytes and renal distal tubules. In enterocytes, the responsible calcium channel is TRPV6. In renal distal tubules, the channel is TRPV5.

Dietary calcium intake is approximately 1 g/d. Approximately 20% is absorbed by the GI tract.

- *Paracellular* absorption does not depend on vitamin D but is based on the favorable intraluminal gradient at the jejunum and ileum when calcium intake is high.
- *Transcellular* absorption occurs primarily in the duodenum when calcium intake is low:
  - Uptake by enterocytes is via the TRPV6 calcium channel, a type of transient receptor potential channel.
  - Cytoplasmic Ca^{2+} is either taken up into the mitochondria or endoplasmic reticulum, transported to the basolateral side via Ca^{2+}-ATPase, or, when intracytoplasmic Ca^{2+} concentrations are high, transported via the Na^{+}-Ca^{2+} exchanger.
  - Calbindin D_{9k} mediates Ca^{2+} transport across enterocytes into the circulation.

Hormonal regulations of GI absorption

- Calcitriol (1,25-$(OH)_2$D [1,25-dihydroxyvitamin D]): 1,25-$(OH)_2$D binds to its receptor (VDR), which increases TRPV6 expression,

calbindin D9k, and Ca^{2+}-ATPase, all acting in concert to increase Ca^{2+} absorption.

- Others: parathyroid hormone (PTH), estrogens, prolactin, growth hormone

Intestinal Ca^{2+} absorption

- Intestinal Ca^{2+} absorption may be increased in acromegaly (growth hormone, calcitriol), pregnancy and puberty (calcitriol), and excess vitamin D ingestion.
- Intestinal Ca^{2+} absorption is decreased with old age; diet with low Ca^{2+}/PO_4^{2-} ratio or high vegetable fiber, fat, or fructose, estrogen deficiency, corticosteroid use; or various medical conditions, including diabetes, kidney failure, and malabsorptive disorders.

Renal handling (Figure 3.2)

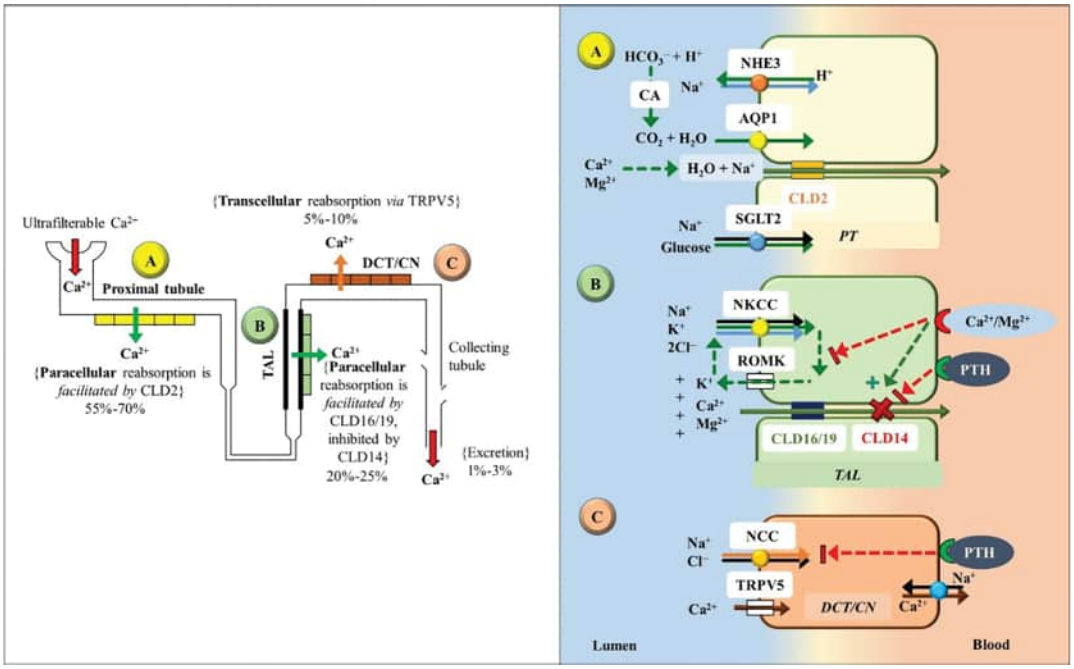


FIGURE 3.2 **Renal handling of calcium.** Ultrafilterable Ca^{2+} load is determined by glomerular filtration rate, glomerular surface, PTH-regulated ultrafiltration coefficient, and acid-base status. A. Ca^{2+} reabsorption follows sodium and water reabsorption paracellularly in the proximal tubules. Anything that reduces Na^+ reabsorption at this segment may lead to calciuria (eg, high dietary Na^+ intake, carbonic anhydrase inhibitor, SGLT2 inhibitor). B. Ca^{2+} reabsorption at the TALH occurs paracellularly, a process facilitated by the claudin-16/19 complex

and inhibited by claudin-14. C. Ca^{2+} reabsorption at the distal convoluted tubules and connecting segment occurs transcellularly via the calcium channel TRPV5. Abbreviations: AQP1, aquaporin 1; CA, carbonic anhydrase; CLD, claudin; DCT/CN, distal convoluted tubule/connecting segment; NCC, sodium chloride cotransporter; NHE3, sodium-hydrogen exchanger; NKCC, sodium-potassium 2 chloride cotransporter; PTH, parathyroid hormone; ROMK, renal outer medullary potassium channel; SGLT2, sodium-glucose cotransporter 2; TAL, thick ascending limb of Henle loop; TRPV5, transient receptor potential cation channel subfamily V.

Glomerular filtration

- Approximately 8 to 10 g of calcium is filtered daily.
- Ultrafilterable Ca^{2+} load is determined by glomerular filtration rate (GFR), glomerular surface, ultrafiltration coefficient K_f, and plasma calcium concentration.
  - PTH reduces glomerular K_f, thereby decreasing the ultrafilterable Ca^{2+} load.
  - Respiratory and metabolic acidoses increase plasma iodized calcium (iCa^{2+}) (due to its release from anions and bones), leading to an increased ultrafilterable Ca^{2+} load and subsequent wasting.

Tubular reabsorption

- Despite the high amount of glomerular filtration of calcium, daily urinary excretion is minimal, that is, 200 mg/d and less, due to effective reabsorption along the entire nephron.
- Proximal tubules (PT)
  - Ca^{2+} is predominantly reabsorbed paracellularly via convection along with NaCl and H_2O. Low intraluminal NaCl in this segment enhances the reabsorption of NaCl and H_2O, and thus Ca^{2+}. Paracellular reabsorption of Ca^{2+} in the PT is facilitated by claudin-2. Variants of claudin 2 have been reported to be associated with increased nephrolithiasis risks.
  - Drugs that reduce proximal tubular Na^+ and Ca^{2+} reabsorption:
    - Any osmotic diuretic agent, for example, mannitol
    - Carbonic anhydrase inhibitors (indirectly inhibit sodium-hydrogen exchanger 3 [NHE3])
    - Sodium-glucose cotransporter type 2 (SGLT2) inhibitors

- Thick ascending limb of Henle loop (TALH):
  - TALH paracellular Ca^{2+} (and Mg^{2+}) reabsorption is driven by the positive luminal charge generated by K^+ recycling at renal outer medullary potassium channel (ROMK) following NaK2Cl reabsorption at sodium-potassium 2 chloride cotransporter (NKCC2).
  - Paracellular Ca^{2+} and Mg^{2+} reabsorption is facilitated by the tight junction protein complex claudin-16/19.
  - Paracellular claudin-14 reduces cation permeability of claudin-16.

FYI

- Variants in claudin 2 and claudin 14 genes have been reported to be associated with increased risk of calcium stones.
- Mutations in claudin 16 and claudin 19 are associated with type I and type II familial hypomagnesemia, hypercalciuria, and nephrolithiasis respectively.

  - Ca^{2+} reabsorption at TALH is regulated by:
    - Calcium-sensing receptor (CaSR): Activation of CaSR by plasma Ca^{2+} inhibits ROMK, thereby reducing intraluminal K^+ recycling and the associated positive charge in the lumen, which in turn decreases paracellular Ca^{2+} reabsorption.
    - PTH: PTH enhances TALH paracellular Ca^{2+} reabsorption by inhibiting claudin-14 expression upon binding to the PTH receptor (PTH1R).
- Distal convoluted tubules and connecting segment (DCT/CN):
  - Luminal uptake of Ca^{2+} occurs transcellularly via the apical TRPV5 calcium channel, followed by extrusion into circulation via basolateral plasma membrane Ca^{2+}-ATPase, Na^+-Ca^{2+} exchanger, and Na^+-Ca^{2+}-K^+ exchanger.
  - Regulation of Ca^{2+} reabsorption at DCT/CN:
    - PTH increases Ca^{2+} reabsorption at the DCT/CN by increasing TRPV5 activity and abundance and inhibiting the sodium chloride cotransporter (NCC). See thiazide-induced hypercalcemia for mechanisms.

- Calcitriol increases TRPV5 expression.
- Potassium (K) channel tetramerization domain containing 1 protein (KCTD1) promotes the differentiation of TALH and DCT cells and modulates Mg^{2+} and Ca^{2+} transport by altering the expression of NCC, NKCC2, claudin-16/19, and claudin-14.

- Calcium is not reabsorbed at collecting ducts.

Regulators of Calcium Homeostasis (Figure 3.3)

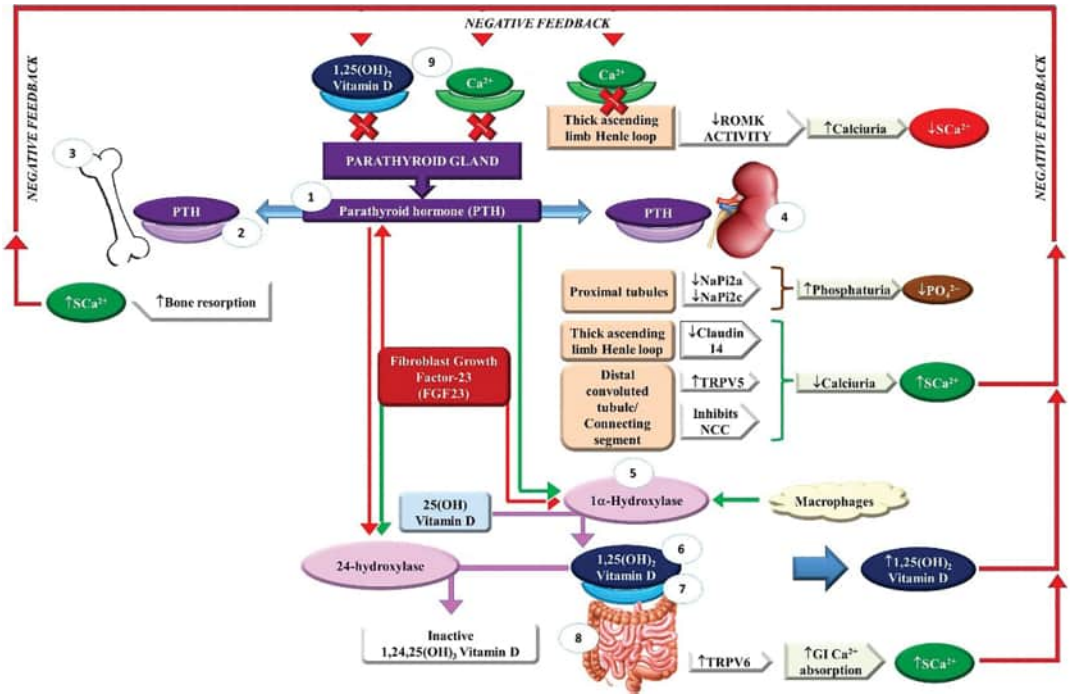


FIGURE 3.3 **Calcium metabolism.** 1. Parathyroid hormone (PTH) is released from parathyroid gland. 2. PTH binds to its receptor PTH1R in bones and kidneys. 3. This leads to increased bone resorption. 4. In kidneys, calcium excretion in the thick ascending limb of Henle loop and distal convoluted tubules/connecting segment is reduced. 5. Additionally, PTH stimulates 1α-hydroxylase, which, 6. hydroxylates $25(OH)D_3$ (calcidiol) to $1,25(OH)_2D_3$ (calcitriol). 7. Calcitriol binds to vitamin D receptors (VDRs), thereby 8. increasing intestinal Ca^{2+} absorption. All effects driven by PTH lead to increased serum Ca^{2+} level. 9. The resulting increase in $1,25(OH)_2D_3$ and Ca^{2+} in turn bind to their respective receptors in the parathyroid gland as negative feedback to reduce parathyroid hormone synthesis and release. Increased Ca^{2+} level also reduces Ca^{2+} reabsorption at the thick ascending limb of Henle loop. Of note, the fibroblast growth factor (FGF23) reduces $1,25(OH)_2D_3$ levels via inhibition of 1α-hydroxylase while stimulating 24-hydroxylase activity. The latter deactivates $1,25(OH)_2D_3$ into $1,24,25(OH)_2D_3$. FGF23 also exerts an inhibitory effect on the parathyroid gland. Green arrows

denote stimulatory effect. Red arrows denote inhibitory effect. Pink arrows denote enzymatic reactions. Red Xs denote negative feedback.
Abbreviations: GI, gastrointestinal tract; Na-Pi, sodium phosphate cotransporter; NCC, sodium chloride cotransporter; ROMK, renal outer medullary potassium channel; SCa^{2+}, serum calcium level; TRPV5, transient receptor potential calcium channel.

Parathyroid hormone

- PTH is the key regulatory hormone to maintain calcium homeostasis.
- PTH binds to its receptor pTHR1 and exerts physiologic effects via bones and kidneys.

PTH effects on bones

- Chronic or prolonged PTH exposure increases bone resorption via increasing the bone-resorption mediator Receptor Activator of NF-kB Ligand (RANKL) while suppressing the secretion of the anti-osteoclastogenesis factor OPG. RANKL is normally secreted by osteoblasts to stimulate osteoclastic proliferation and activity thereby increasing bone resorption.
- Intermittent increase or administration of PTH increases bone mass via increasing osteoblast proliferation and survival.

PTH effects on kidneys

- TALH: PTH increases paracellular Ca^{2+} reabsorption via inhibition of claudin-14 expression.
- DCT/CN: PTH increases transcellular Ca^{2+} reabsorption by increasing apical expression of the calcium channel TRPV5 and reducing NCC activity.
- PTH increases 1α-hydroxylase activity. 1α-Hydroxylase hydroxylates 25(OH)D to $1,25(OH)_2D$. The latter promotes intestinal Ca^{2+} absorption.
- PTH inhibits 24-hydroxylase activity: This enzyme hydroxylates carbon 24 of vitamin D and renders it inactive.
- PTH also induces phosphaturia by suppressing the transcriptions of genes encoding proximal tubular sodium phosphate transporters NPT2a and NPT2c that normally function to reabsorb luminal phosphate.

Regulators of PTH

- Inhibitory factors:
  - $1,25(OH)_2D$ inhibits parathyroid cells via binding to vitamin D receptor (VDR).
  - Extracellular iCa^{2+} inhibits parathyroid cells upon binding to CaSR.
  - Fibroblast growth factor-23 (FGF23) inhibits PTH transcription and secretion.
- Stimulatory factors:
  - Hypocalcemia
  - Hypovitaminosis D
  - Hyperphosphatemia

Calcium-sensing receptor

Proximal tubules

- In PT, CaSR is expressed on the luminal side. Upon activation, CaSR:
  - Stimulates NHE3 activity
    - NHE3 increases Na^+ and HCO_3^- reabsorption. Accumulation of solutes and electrolytes at the basolateral side of proximal tubular cells generates an osmotic driving force for transcellular and paracellular transport of luminal water along with electrolytes and iCa^{2+} into the interstitium.
    - Increased NHE3 activity also contributes to urine acidification (via increasing HCO_3^- reabsorption), thereby minimizing calcium phosphate stone formation in the setting of hypercalciuria.

Thick ascending limb of Henle loop

- In TALH, CaSR is expressed on basolateral side.
- At TALH, activation of CaSR:
  - Inhibits apical K^+ recycling at ROMK, thereby reducing paracellular Ca^{2+}/Mg^{2+} reabsorption
  - Modulates claudin-14

Distal convoluted tubule

In DCT, apical CaSR increases NCC activity, thereby limiting Ca^{2+} reabsorption.

Collecting ducts

- In collecting ducts, activation of apical CaSR is thought to be protective against calcium stone formation by:
  - Reducing vasopressin-mediated trafficking and expression of apical aquaporin-2, thereby increasing urine flow
  - Increasing NHE3 activity to acidity the urine

Vitamin D (Figure 3.4)

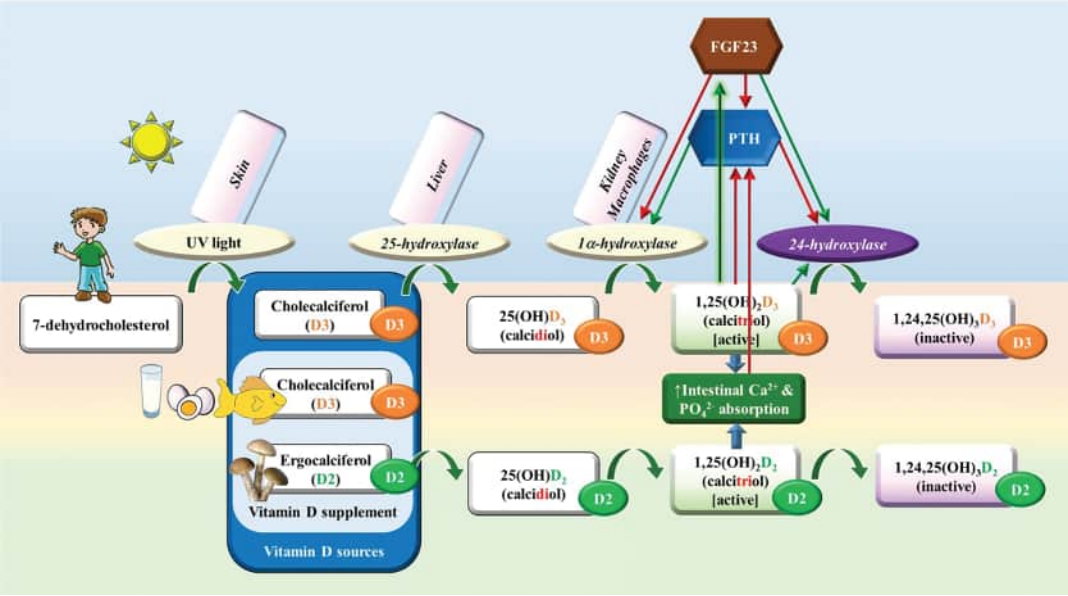


FIGURE 3.4 **Vitamin D metabolism.** D2 and D3 refer to the source of vitamin D: D2 is plant-based, whereas D3 is animal- or human-derived. "Diol" and "triol" refer to the number of OH groups present on vitamin D. Both cholecalciferol and ergocalciferol have one OH group. 25-Hydroxylation by the liver converts these molecules into "diol" and subsequent 1α-hydroxylation by the kidneys converts them into "triol." Red arrows denote inhibitory effect. Green arrows denote stimulatory effect. Pink arrows denote enzymatic conversion.
Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxy-vitamin; 25(OH)D, 25-hydroxy-vitamin D; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; UV, ultraviolet.

- Ultraviolet (UV) light (skin exposure) converts 7-dehydrocholesterol to cholecalciferol.
- Liver hydroxylates cholecalciferol at the 25-carbon to 25(OH)D (via 25-hydroxylase).

- Kidney hydroxylates 25(OH)D (via 1α-hydroxylase) to $1,25(OH)_2D$. This is calcitriol, the most biologically active form of vitamin D.
- 24-Hydroxylation of $25(OH)_2D$ or $1,25(OH)_2D$ (by 24-hydroxylase) to $24,25(OH)_2D$ or $1,24,25(OH)_3$-vitamin D, respectively, renders vitamin D inactive.
  - Overactivity of 24-hydroxylase leads to $1,25(OH)_2D$ deficiency.
  - Loss-of-function mutation of 24-hydroxylase leads to $1,25(OH)_2D$ excess.
  - Regulation of 24-hydroxylase:
    - PTH decreases 24-hydroxylase activity.
    - Vitamin D receptor agonist (VDRA), that is, $1,25(OH)_2D$, increases 24-hydroxylase activity.
    - FGF23 increases 24-hydroxylase activity while decreasing 1α-hydroxylase activity. The former inactivates $1,25(OH)_2D$, while the latter reduces $1,25(OH)_2D$ formation. Essentially, FGF23 is "anti" $1,25(OH)_2D$.
- Other regulators of vitamin D synthesis:
  - $1,25(OH)_2D$ synthesis is increased during puberty, pregnancy, and lactation.
  - Mg^{2+} is an essential cofactor for vitamin D synthesis and activation and, vitamin D, in turn, can increase intestinal Mg^{2+} absorption.
- Physiologic effects of $1,25(OH)_2D$:
  - Increases intestinal absorption of calcium and phosphate
  - Provides negative feedback on PTH via:
    - Reducing PTH gene transcription
    - Increasing VDR and CaSR expressions on parathyroid cells
    - Reducing parathyroid cell proliferation
  - Regulates various cellular functions involving the immune and cardiovascular systems and the differentiation, proliferation, and apoptosis of normal and malignant cells

FGF23 and Klotho

Background

- FGF23 is a peptide produced by osteocytes and osteoblasts.
- Transmembrane αKlotho (Klotho) is highly expressed in the kidney and functions as a coreceptor for FGF receptors (FGFRs) to activate FGF23 signaling pathway.
  - The extracellular domain of Klotho can be enzymatically cleaved and released into circulation as soluble Klotho.
  - Soluble Klotho weakly activates FGFRs to transduce the FGF23 signaling pathway and functions as an enzyme and hormone in a variety of biologic roles.
- FGF23 exerts its biologic effects through activation of FGFRs in a Klotho-dependent manner. Nonetheless, extremely high FGF23 can exert its pathologic effect independent of Klotho.

Physiologic roles of FGF23

- Induces phosphaturia by suppressing proximal tubular NPT2a and NPT2c expressions
- Reduces $1,25(OH)_2D$ activity via inhibition of 1α-hydroxylase and stimulation of 24-hydroxylase activity
- Inhibits PTH
- Increases Na^+ and Ca^{2+} reabsorption by increasing apical membrane expression of TRPV5 and NCC

Regulatory factors of FGF23

FGF23 is upregulated by $1,25(OH)_2D$ and high phosphate "burden" (ie, high dietary phosphate intake and not necessarily actual hyperphosphatemia). In early chronic kidney disease (CKD), FGF23 level increases prior to the rise in PTH level.

Clinical significance of FGF23

- The decline in serum and urinary Klotho, followed by a rise in serum FGF23, portends kidney dysfunction and predicts an increased risk of cardiovascular disease (CVD) and mortality in both patients with CKD and the general population.
- Increased FGF23 level has been shown to be associated with:

- Increased mortality in critically ill patients, with and without acute kidney injury (AKI)
- Left ventricular hypertrophy, heart failure, volume status in patients with end-stage kidney disease (ESKD)
- Bone loss and increased fracture risk in both CKD and non-CKD
- Infectious complications, increased inflammatory cytokines
- Reduced erythropoiesis (anemia of CKD)
- Greater increase in height-adjusted total kidney volume and rate of decline in eGFR in patients with autosomal dominant polycystic kidney disease
- Increased risk of CKD progression

Metabolic acidosis-induced calciuria

- Release of skeletal calcium phosphate to buffer H^+
- Reduction in osteoblastic relative to osteoclastic activity
- Protein-activated ovarian cancer G-protein (OGR1): OGR1 is a pH sensor that can induce hypercalciuria in metabolic acidosis by controlling NHE3 activity in PT.

Sclerostin

- Sclerostin is an osteocyte-derived hormone that has antianabolic effects on bones.
- Mutations involving sclerostin or its transcription result in increased bone mass.
- Sclerostin synthesis is downregulated by PTH, mechanical loading, and estrogen, and is stimulated by calcitonin and steroids.
- Romosuzomab, an antisclerostin antibody, is FDA approved for postmenopausal women with osteoporosis with mild to moderate CKD

Miscellaneous

- Testosterone upregulates the expression of renal senescence marker protein-30 (SMP30), a calcium-binding protein, and increases renal

tubular Ca^{2+} reabsorption via plasma membrane calcium ATPase-4.

- Aging has reduced testosterone and SMP30 levels.
- Lactation increases expression of TRPV5 and calbindin 1.
- Adiponectin, an insulin-sensitizing adipokine, is associated with bone loss. Adiponectin modulates tubular transport of Ca^{2+} and phosphate, a process partially mediated by Klotho.

Calcium Intake and Cardiovascular Outcomes

2021 meta-analysis

- Thirteen double-blind, randomized placebo-controlled trials (RCTs) (*n* = 28,935 participants in an intervention group and 14,243 in a control group)
- Calcium supplements significantly increased the risk of CVD (RR 1.15, 95% CI 1.06-1.25) and coronary heart disease (CHD) (RR 1.16, 95% CI 1.05-1.28), specifically in women who are healthy and postmenopausal.
- In the subgroup meta-analysis, dietary calcium intake of 700 to 1,000 mg/d or supplementary calcium intake of 1,000 mg/d significantly increased the risk of CVD and CHD. Calcium supplements increased the risk of CVD by about 15% in healthy postmenopausal women. No significant association was found between the use of calcium supplements and the risk of cerebrovascular disease.

HYPERCALCEMIA

Pseudohypercalcemia

- Total serum calcium level is elevated, but ionized calcium level is within normal range.
- This can be seen when there is increased protein-bound calcium (eg, excessive albumin infusion or paraproteinemia).

Causes of True Hypercalcemia

Conditions associated with true hypercalcemia are summarized in **Table 3.1**.

Table 3.1 Hypercalcemic disorders as they correspond to different levels of calcium metabolism

Calcium homeostasis factors	Corresponding abnormalities leading to hypercalcemia	Expected laboratory findings (in addition to hypercalcemia)
1. PTH	• Parathyroid hyperplasia, adenoma, carcinoma • PTHrp (paraneoplastic syndrome, pregnancy) • Drug-induced hyperparathyroidism: lithium • Drug-induced skeletal resistance to PTH leading to hPTH: sunitinib and imatinib	• Hypophosphatemia • ↑PTH and ↑1,25$(OH)_2$D • If ↑PTHrp, PTH would be ↓ • Hypercalciuria; phosphaturia
2. PTH1R	PTH1R gain-of-function mutation (Jansen disease)	• Hypophosphatemia • ↑1,25$(OH)_2$D; ↓PTH • Hypercalciuria; phosphaturia
3. Bones	• Metastatic malignancy • Presence of osteoclastic activating factors (PTHrp, growth factors, cytokines) • Drug induced (excess vitamin A ingestion) • Immobilization • Paget disease	• Normo- to hyperphosphatemia • ↓PTH; ↓1,25$(OH)_2$D • Hypercalciuria

4. Kidneys	• TAL: loss-of-function mutation of CaSR (familial hypocalciuric hypercalcemia)
	• DCT/CN: thiazide diuretics; amiloride
		• Loss-of-function mutation of CaSR:
		  • ↑PTH; ↑1,25$(OH)_2$D
		  • Hypocalciuria; phosphaturia
		• DCT/CN (thiazides, amiloride):
		  • ↓PTH; ↓1,25$(OH)_2$D
		  • Hypocalciuria

Calcium homeostasis factors	Corresponding abnormalities leading to hypercalcemia	Expected laboratory findings (in addition to hypercalcemia)
5. 1α-Hydroxylase activity	• Granulomatous disease • Loss-of-function mutation of 24-hydroxylase • Loss-of-function mutation of FGF23	• Normo to hyperphosphatemia • ↑1,25$(OH)_2$D; ↓PTH • Hypercalciuria
6. 1,25$(OH)_2$D level	• Tumor-producing calcitriol (lymphomas, leiomyoblastoma) • Vitamin supplements	• Normo- to hyperphosphatemia • ↑1,25$(OH)_2$D; ↓PTH • Hypercalciuria
7. 1,25$(OH)_2$D receptor (VDR)	Gain-of-function mutation of VDR	• Normo- to hyperphosphatemia • ↓1,25$(OH)_2$D; ↓PTH
8. Gastrointestinal tract	Excess calcium ingestion	• Normo- to hyperphosphatemia (milk-alkali); hypophosphatemia (Calcium carbonate may act as phosphate binder if taken with meals.) • ↓1,25$(OH)_2$D; ↓PTH • Hypercalciuria
9. Calcium sensing receptor (CaSR)	• Loss-of-function mutation of CaSR (familial hypocalciuric hypercalcemia) • Autoantibodies to CaSR	• ↑PTH; ↑1,25$(OH)_2$D • Hypocalciuria; phosphaturia

Refer to Figure 3.5 for corresponding levels of calcium regulation.

Abbreviations: DCT/CN, distal convoluted tubule/connecting segment; FGF23, fibroblast growth factor-23; PTH, parathyroid hormone; PTH1R, parathyroid hormone receptor 1; PTHrp, parathyroid hormone related peptide; TAL, thick ascending limb of Henle loop; VDR, vitamin D receptor

Primary hyperparathyroidism (pHPT) with hypercalcemia

- Patients present with elevated PTH levels and hypercalcemia.
- Etiology: parathyroid adenoma (80%), diffuse hyperplasia (10%-15%) or carcinoma (5%)

Primary hyperparathyroidism with normocalcemia

- Patients present with elevated PTH levels but normal serum calcium level.
- Diagnosis of normocalcemic pHPT is a diagnosis of exclusion. The following secondary causes of pHPT must be ruled out:
  - Conditions that could directly stimulate PTH secretion (eg, vitamin D deficiency, malabsorptive disorders, primary hypercalciuria, CKD, metabolic bone diseases, lithium use, tyrosine kinase inhibitors [sunitinib, imatinib])
  - Conditions that could induce mild hypocalcemia and result in increased PTH secretion (eg, use of bisphosphonate or denosumab)
- Prevalence of kidney stones, low bone mineral density, and HTN in patients with normocalcemia pHPT has been reported to be similar to those with hypercalcemic pHPT.

Primary hyperparathyroidism with normal PTH (normohormonal pHPT)

- Patients with pHPT who present with elevated SCa levels but normal PTH level
- Clinical manifestations have been reported to be similar to those with classic pHPT, except for greater rate of kidney stones.

Multiple endocrine neoplasia type 1 (MEN-1)

- MEN-1: autosomal dominant inactivating germline mutation of a tumor-suppressor gene (MEN-1 gene) that may involve parathyroid, anterior pituitary, enteropancreatic, and other endocrine tumors
- Multiple endocrine neoplasia type 2A (MEN-2A): autosomal dominant activating mutation of the RET proto-oncogene that may involve thyroid medulla, adrenal medulla, parathyroid with associated increase in calcitonin, catecholamines, and PTH

Parathyroid hormone–related peptides (PTHrP)

Hypercalcemia of pregnancy

- PTHrP is produced from mammary and placental tissues in response to prolactin receptor activation.
- Treatment: bromocriptine

Paraneoplastic syndromes

PTHrP release may be associated with breast cancer and squamous cell lung carcinoma.

Gain-of-function mutation of the PTH1R: Jansen disease

- Rare hereditary condition due to activating mutation of the PTH1R
- Clinical manifestations: short-limbed dwarfism, severe hypercalcemia, hypophosphatemia, metaphyseal chondrodysplasia

Increased bone resorption

Malignancy

- Direct invasion (bone metastatic disease)
- PTHrP released from bone by osteolytic metastases
- Increased PTH (parathyroid carcinoma)
- Ectopic PTH production (ovarian carcinoma, neuroendocrine tumors)
- Increased calcitriol production by tumor cells (diffuse large B-cell lymphoma) or by adjacent macrophages
- Osteoclastic-activating factors, including interleukins (IL-1, IL-6), prostaglandins, transforming growth factors, and tumor necrosis factor-α
- Immobilization (increased osteocyte synthesis of sclerostin, which inhibits bone formation and simultaneously stimulates bone resorption)

Paget disease of bone

Excessive bone resorption followed by increased bone formation and sclerosis. Pathogenesis unclear

Thyrotoxicosis

Increased 1α-hydroxylase activity

Granulomatous diseases (eg, tuberculosis, sarcoid, berylliosis)

- Due to increased 1α-hydroxylase activity in macrophages within granulomas
- Sarcoid may increase plasma Ca^{2+} further with high sun exposure.
- Laboratory findings: low PTH, elevated $1,25(OH)_2D$
- Fungal infection (*Pneumocystis jirovecii*, *Histoplasma capsulatum*, microsporidium)
- Silicone and polymethylmethacrylate infections for cosmetic purposes

Reduced FGF23 activity

Although reduced FGF23 activity lifts its inhibitory effect on 1α-hydroxylase, thereby increasing $1,25(OH)_2D$ levels, the latter inhibits PTH and results in calciuria. Plasma calcium level, therefore, may not be elevated.

Loss-of-function mutation of 24-hydroxylase

- Loss-of-function mutation of 24-hydroxylase leads to high levels of $1,25(OH)_2D$, hence hypercalcemia. Both $1,25(OH)_2D$ and hypercalcemia, in turn, suppress PTH.
- Resultant phenotype: hypercalcemia with associated nephrocalcinosis or nephrolithiasis
- Treatment: Ketoconazole (inhibitor of 1α-hydroxylase) corrects hypercalcemia. In contrast to patients with hypercalcemia secondary to excess $1,25(OH)_2D$, corticosteroids do not ameliorate hypercalcemia in patients with inactivating 24-hydroxylase.

Increased $1,25(OH)_2D$

- Tumor-associated: lymphomas (both Hodgkin and non-Hodgkin), ovarian dysgerminomas, leiomyoblastoma, among others. In malignancy-associated $1,25(OH)_2D$-induced hypercalcemia, cancer cells may recruit and stimulate adjacent macrophages to express 1α-hydroxylase. Other mechanisms are possible and remain to be elucidated.

- Vitamin D supplements

Loss-of-function mutation of CaSR: familial hypocalciuric hypercalcemia (FHH)

- A rare autosomal dominant hereditary condition due to inactivating mutations in the gene encoding CaSR. In the TALH, CaSR senses hypercalcemia and inhibits ROMK, thereby affecting luminal K^+ recycling and the loss of the positive luminal charge that facilitates paracellular Ca^{2+} reabsorption. Whereas normal activation of CaSR induces calciuria, inactivating mutation of CaSR reduces calciuria, resulting in hypercalcemia. In most cases, FHH is benign without complications from hypercalcemia.
- Laboratory findings:
  - Moderate chronic hypercalcemia; normo- to hypophosphatemia due to elevated PTH; normo- to hypermagnesemia due to increased TALH paracellular reabsorption
  - Elevated PTH levels: Under normal conditions, activation of CaSR inhibits PTH secretion. Inactivating mutation of CaSR allows for uninhibited PTH secretion, hence elevated PTH levels. This explains why FHH may be mistaken for pHPT.
  - $1,25(OH)_2D$ level may be high in response to elevated PTH levels.

NOTE

- Fractional calcium excretion is low (eg, <0.01) in FHH but high in pHPT. This is the differentiating point between FHH and pHPT. In general, parathyroidectomy should not be performed if hypercalcemia is due to FHH. In FHH with severe hypercalcemia-associated complications, total (not partial) parathyroidectomy may be necessary.
- Fractional excretion of calcium may be calculated as 24-hour calcium clearance divided by 24-hour creatinine clearance, which is referred to as "calcium-to-creatinine clearance ratio" (CCCR).

$$CCCR = [(\text{urine calcium}) \times (SCr)] \div [(\text{urine creatinine}) \times (SCa)]$$

- CCCR <0.010 indicates FHH, whereas a CCCR more than 0.020 suggests pHPT.

- Treatment: Calcimimetics may be beneficial in some patients.

- Some patients with the diagnosis of HPT have been found to have autoantibodies to CaSR. These patients may have similar presentations as those with FHH.

Ingestions

Calcium-containing products (calcium carbonate, Nicorette gum, calcium supplemented bottled carbonated water, etc)

Milk-alkali syndrome refers to the triad of hypercalcemia, metabolic alkalosis, and AKI associated with the ingestion of large amounts of calcium and absorbable alkali (eg, calcium-fortified milk + sodium bicarbonate). Treatment of milk-alkali syndrome with furosemide may lead to transient hypocalcemia, with an associated rebound rise in PTH to supranormal levels.

Excessive vitamin D (over-the-counter vitamin supplements)

Thiazides and amiloride

- The relative volume depletion associated with thiazide diuretic use may increase proximal tubular Ca^{2+} reabsorption.
- The inhibition of Na^{+} reabsorption by thiazides/amiloride at the DCT/CN, respectively, hyperpolarizes the membrane voltage, thereby facilitating Ca^{2+} influx. This effect has been shown to be inhibited by dihydropyridine-type calcium channel blockers (CCB).

Others: lithium (may lead to hyperparathyroidism), antacids (calcium carbonate—patients present with both hypercalcemia and metabolic alkalosis), vitamin A overload (increased bone resorption)

Clinical Manifestations of Hypercalcemia

- Fatigue, poor concentration, headaches, depression, anxiety
- Ocular: conjunctivitis, band keratopathy
- Cardiac: shortened QT, arrhythmias

NOTE

An ST-like elevation may be seen on electrocardiogram (ECG) (as the T wave moves closer to the QRS wave) in patients with severe hypercalcemia and may be mistaken as acute myocardial infarction.

- GI tract: constipation, nausea, vomiting, peptic ulcer disease, pancreatitis
- Kidneys: polyuria, nephrogenic diabetes insipidus, kidney stones, medullary and cortical calcium depositions (nephrocalcinosis)

Management of Hypercalcemia

General considerations

- Volume repletion with normal saline as tolerated
- Loop diuretics may be added once euvolemic or hypervolemic to enhance paracellular Ca^{2+} excretion from TALH.

Bisphosphonates

- Inhibit bone resorption and calcitriol synthesis
- Preferred agents for hypercalcemia associated with cancer
- Commonly used agents:
  - Intravenous pamidronate, oral alendronate, clodronate
  - Calcitonin: rapid onset of action (within hours), but only short-term benefit due to tachyphylaxis
- Zoledronic acid has been used successfully in patients with sarcoid-induced hypercalcemia and may become first-line agent for this indication (contraindicated for eGFR <35 mL/min/1.73 m^2).
- Mithramycin: cytostatic drug
  - Potent inhibitor of bone resorption
  - Rapid onset of action, effect lasts days, but high adverse effects (transaminitis, thrombocytopenia)

Prostaglandin antagonist

- The use of aspirin and indomethacin has been reported to successfully ameliorate malignant hypercalcemia (case reports).
- Mechanism is throught to involve tumor-produced prostaglandin mediated hypercalcemia.

Corticosteroids (0.5-1.0 mg/kg prednisone daily)

- Reduces GI absorption of calcium
- May be used in hypervitaminosis D (either endogenous source such as sarcoid/granulomatous diseases or exogenous vitamin D ingestion)
- May be considered in lymphoproliferative malignancies such as lymphoma, multiple myeloma, or even solid organ malignancy such as breast CA

Ketoconazole

- Inhibits calcitriol synthesis via inhibition of 1α-hydroxylase
- May be used for patients with vitamin D-24-hydroxylase loss-of-function mutation. Corticosteroid is ineffective in these patients.

Calcimimetics

- CaSR agonists such as cinacalcet, etelcalcetide
- May be used for hyperparathyroidism (primary, secondary, or even parathyroid carcinoma), particularly for nonsurgical candidates

Denosumab

- Denosumab (Prolia, Xgeva) is a human mAb that binds to and inhibits the bone-resorption mediator Receptor Activator of NF-kB Ligand (RANKL). RANKL is normally secreted by osteoblasts to stimulate osteoclastic proliferation and activity (increase bone resorption). Inhibition of RANKL by denosumab inhibits osteoclastic activity.
- Denosumab may ameliorate malignancy-associated hypercalcemia due to bone involvement.
- May cause severe hypocalcemia in patients with ESKD and should be avoided

Parathyroidectomy for pHPT refractory to medical therapies

Indications

- Age below 50 due to eventual significant complications if left untreated over lifetime
- SCa greater than 1.0 mg/dL or iCa^{2+} greater than 0.12 mmol/L above upper limit of normal
- Marked bone density reduction with *T*-score −2.5 or less at lumbar spine, femoral neck, total hip, or the 1/3 radius for postmenopausal women or men above 50 years of age
- GFR less than 60 mL/min
- Others: hypercalciuria more than 400 mg/d or kidney stones, patient surgical preference due to difficult/impossible follow-up

Complications

- Hungry bone syndrome: defined as having profound (SCa <6 mg/dL) and prolonged (>4 days postoperative) hypocalcemia along with hypophosphatemia and hypomagnesemia following parathyroidectomy
  - Pathogenesis: Continuing increased skeletal calcium uptake for bone formation without the opposing calcium leak from bone resorption due to the acute fall in PTH following parathyroidectomy
  - Risks: severe hyperparathyroidism with associated skeletal manifestations, preoperative indices of high bone turnover (high PTH and alkaline phosphatase, low serum calcium), osteitis fibrosa cystica, and/or "brown tumors"
- Hyperkalemia is commonly reported following parathyroidectomy. Mechanism is unknown.

Management

- Intravenous calcium supplement (6-12 g/d), followed by oral therapy when safe, plus
- Calcitriol (2-4 µg/d), plus
- Correction of hypomagnesemia
- Preoperative repletion of vitamin D and use of bisphosphonates (eg, intravenous administration of pamidronate 30 mg daily × 2 consecutive days or single dose of 60 mg) have been suggested to ameliorate postoperative hungry bone syndrome.

Others

- Propranolol may be used for thyrotoxicosis-induced hypercalcemia.
- Estrogen may be considered in women with pHPT. Estrogen increases GI calcium absorption and reduces bone resorption.

HYPOCALCEMIA

Causes of Hypocalcemia

Pseudohypocalcemia

Acute respiratory alkalosis or severe metabolic alkalosis: Clinically significant reduction in ionized Ca^{2+} may occur due to increased Ca^{2+} complexing to the increased levels of organic anions associated with alkalemia. Free ionized Ca^{2+} level is low, but total serum calcium levels remain the same.
Hypoalbuminemia: low total serum calcium with normal ionized Ca^{2+} levels due to reduced albumin-bound calcium fraction

True hypocalcemia

Conditions associated with true hypocalcemia are summarized in **Table 3.2.**

Table 3.2 Hypocalcemic disorders as they correspond to different levels of calcium metabolism

Calcium homeostasis factors	Corresponding abnormal calcium regulation leading to hypocalcemia	Expected laboratory findings (in addition to hypocalcemia)
1. PTH	• Parathyroidectomy • Resistance to PTH (Albright renal osteodystrophy, Mg^{2+} deficiency)	Normo- to hyperphosphatemia; ↓PTH (↑PTH if PTH resistance); ↓$1,25(OH)_2D$
2. PTH1R	Loss-of-function mutation of PTH1R (Blomstrand chondrodysplasia, primary failure of tooth eruption)	↑PTH; ↓$1,25(OH)_2D$

Calcium homeostasis factors	Corresponding abnormal calcium regulation leading to hypocalcemia	Expected laboratory findings (in addition to hypocalcemia)
3. Bones	Increased bone formation "hungry bone syndrome"	Normo- to hypophosphatemia; ↓PTH and ↓1,25$(OH)_2$D

4. Kidneys	Increased renal Ca^{2+} excretion:
	• TAL:
	  • Gain-of-function mutation of CaSR
	  • CaSR agonists (cinacalcet, etelcalcetide)
	• DCT/CN:
	  • Loss-of-function mutation of TRPV5
		• TAL-activating mutation of CaSR:
		  • ↓PTH due to continuing negative feedback; ↓1,25$(OH)_2$D
		  • Variable phosphate levels
		  • Hypercalciuria
		• DCT/CN: ↓TRPV5 activity
		  • ↑PTH; ↑1,25$(OH)_2$D
		  • Hypercalciuria; phosphaturia

5. 1α-Hydroxylase activity	• Reduced 1α-hydroxylase activity • Gain-of-function mutation of 24-hydroxylase • Any mutation leading to ↑FGF23 activity	• ↓1,25$(OH)_2$D; ↑PTH • Hypophosphatemia

6. 1,25$(OH)_2$D level	• Reduced 1,25$(OH)_2$D levels:
	  • Severe malnutrition; malabsorption
	  • Kidney failure
	• Deficiency of 1,25$(OH)_2$D precursors:
	  • Severe lack of sun exposure
	  • Liver failure
		• ↓1,25$(OH)_2$D; ↑PTH
		• Hypophosphatemia

7. 1,25$(OH)_2$D receptor (VDR)	Loss-of-function mutation of VDR	• ↑1,25$(OH)_2$D level; ↑PTH • Normo- to hypophosphatemia
8. Gastrointestinal tract	Severe malnutrition (low calcium intake)	• ↑PTH; ↑1,25$(OH)_2$D • Hypophosphatemia

Calcium homeostasis factors	Corresponding abnormal calcium regulation leading to hypocalcemia	Expected laboratory findings (in addition to hypocalcemia)
9. Calcium sensing receptor (CaSR)	• Gain-of-function mutation of CaSR • CaSR agonists (cinacalcet, etelcalcetide)	• ↓PTH; ↓1,25(OH)$_2$D • Hyperphosphatemia • Hypercalciuria
10. Other	Systemic tissue calcifications: • Acute pancreatitis • Rhabdomyolysis	• ↑PTH; ↑1,25(OH)$_2$D • Hypophosphatemia (likely due to compensatory hyperparathyroidism) • Hyperphosphatemia if rhabdomyolysis

Refer to Figure 3.3 for corresponding levels of calcium regulation.

Abbreviations: DCT/CN, distal convoluted tubule/connecting segment; FGF23, fibroblast growth factor-23; PTH, parathyroid hormone; PTH1R, parathyroid hormone receptor 1; PTHrp, parathyroid hormone related peptide; TAL, thick ascending limb of Henle loop; TRPV5, transient receptor potential calcium channel; VDR, vitamin D receptor.

Hypoparathyroidism

May be seen in patients with neck irradiation, amyloid infiltration of parathyroid glands, idiopathic, sporadic, or postoperative hypoparathyroidism

Resistance to PTH

- Resistance to PTH can lead to compensatory increase in PTH levels.
  - Magnesium deficiency reduces PTH synthesis and release and induces skeletal resistance to PTH.
  - Drug-induced: tyrosine kinase inhibitors sunitinib and imatinib
  - Inactivating mutation of PTH receptor PTH1R: very rare condition known as Blomstrand chondrodysplasia and primary failure of tooth eruption
  - Albright hereditary osteodystrophy: a condition linked to maternally inherited inactivating *GNAS1* mutations, where patients present with short fourth and fifth metacarpals, rounded facies, and resistance to PTH

- Laboratory findings: hypocalcemia, hyperphosphatemia, low $1,25(OH)_2D$, high PTH level

Increased bone formation

Hungry bone syndrome due to reduced bone resorption relative to bone formation (can be seen following parathyroidectomy)

Increased renal calcium excretion

Autoantibody formation against claudin-16 has been reported in a patient with severe magnesium wasting, hypocalcemia, and tubulointerstitial chronic nephropathy, who was later diagnosed with renal carcinoma expressing high levels of claudin-16.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: Mutations in claudin-16 and claudin-19 manifest as TALH paracellular Ca^{2+} and Mg^{2+} wasting.

Activating mutation of CaSR

- CaSR are expressed in both kidneys and parathyroid gland. Any mutation or agent affecting CaSR will affect both organs. Clinical manifestations associated with altered CaSR activity must be considered for both kidneys and parathyroid gland.
- Renal effect: hypocalcemia (hypercalciuria) and hypomagnesemia (hypermagnesuria)
- Parathyroid gland effect: PTH cellular proliferation and activity are suppressed. Reduced PTH secretion leads to hyperphosphatemia and reduced $1,25(OH)_2D$ level. The latter also contributes to hypocalcemia.

Loss-of-function mutations of TRPV5

Drug-induced: calcimimetics, loop diuretics

Reduced $1,25(OH)_2D$ activity

- Notable laboratory findings: hypocalcemia, elevated PTH, hypophosphatemia due to reduced intestinal absorption of both Ca^{2+} and PO_4^{2-} and PTH-induced phosphaturia
- Vitamin D resistance due to mutations of VDR

- Kidney failure (labs as above, except PO_4^{2-} level is normal to high)

Reduced intestinal calcium absorption independent of vitamin D levels

- Malabsorptive syndromes
- Malnutrition

Systemic tissue calcium sequestration

- Associated conditions: acute pancreatitis, rhabdomyolysis
- Treatment of these conditions is reserved for moderate-to-severe hypocalcemia (eg, presence of neurologic symptoms or ECG changes such as prolonged QT, tetany) because:
  - Hypocalcemia is transient. Sequestered Ca^{2+} will be released back into circulation with recovery.
  - PTH is stimulated during the hypocalcemic phase and can contribute to recovery phase "overshoot" hypercalcemia.
  - Calcium infusion in the presence of hyperphosphatemia (seen with rhabdomyolysis) may facilitate intravascular and soft tissue calcifications.
  - Hypercalcemia from calcium infusion can lead to intracellular calcium accumulation, which may promote acinar injury and cell death in pancreatitis.

Miscellaneous (mechanism unclear)

Programmed cell death protein 1 (PD1) inhibitors are associated with hypocalcemia, AKI, and tubulointerstitial nephritis with pooled incidence rates of 1%, 2.2%, and 16.6%, respectively.
Tyrosine kinase inhibitors (sorafenib): Hypocalcemia is observed in up to 10%.

Diagnosis of Hypocalcemia

Calcium-to-creatinine clearance ratio

Ratios more than 0.020 can be seen in all forms of hyperparathyroidism, elevated PTHrP, and renal Ca^{2+} wasting conditions (eg, activating mutation of CaSR, post-AKI diuresis, diuretics, and severe CKD).

Urinary calcium excretion *during treatment with calcium and vitamin D derivatives*

- Urinary calcium excretion will increase with treatment in patients with hypoparathyroidism and renal calcium wasting conditions. Nephrocalcinosis may be a complication.
- Urinary calcium will be low in patients with other causes of hypocalcemia.

Urinary phosphate excretion

- Expected to be high in vitamin D deficiency (due to increased PTH)
- Expected to be low in hypoparathyroidism, pseudohypoparathyroidism, magnesium deficiency (due to associated hypoparathyroidism)

Intracranial calcifications

Intracranial calcifications, particularly within basal ganglia, are observed more frequently in idiopathic hypoparathyroidism compared with other forms of hypoparathyroidism.

Management of Hypocalcemia

Calcium supplement

Correct the underlying etiology whenever possible.

- Indications for intravenous calcium:
  - Severe neuromuscular symptoms (eg, seizures, neuromuscular spasm), prolonged QT
  - Asymptomatic or mild symptoms (eg, paresthesias), acute hypocalcemia with serum calcium level 7.5 mg/dL or less (1.9 mmol/L) or ionized calcium 3 mg/dL or less (0.8 mmol/L), or

having greater serum calcium levels but cannot tolerate oral calcium

  - Note that intravenous calcium gluconate is generally preferred over calcium chloride ($CaCl_2$) because the former is less irritating to veins. Additionally, it should be cautioned that 1 g of $CaCl_2$ contains 272 mg (13.2 mEq) of elemental calcium compared with 94 mg (4.7 mEq) for 1 g of calcium gluconate.
- For mild and asymptomatic hypocalcemia, provide oral calcium.
- Supplement magnesium if low.

Thiazide diuretics

Thiazide diuretics may be used concurrently with calcium supplementation in patients with hypoparathyroidism to reduce urinary calcium excretion and nephrocalcinosis. As with calcium stone management, high fluid intake and low sodium intake should be advised.

Vitamin D supplement

Calcitriol, 1α-hydroxycholecalciferol, or paricalcitol are the treatment of choice for idiopathic or acquired hypoparathyroidism because they can minimize large calcium supplement.

NOTE

- In the case of concurrent acidemia and severe hypocalcemia, correct hypocalcemia FIRST. Do NOT correct acidemia prior to the correction of hypocalcemia. Alkalinization reduces ionized Ca^{2+} levels and may precipitate life-threatening neurologic and/or arrhythmias.
- Calcium CANNOT be given in the same intravenous line as sodium bicarbonate due to calcium precipitation as calcium carbonate.

DISORDERS OF PHOSPHATE METABOLISM

Background

- Up to 99% of total body phosphates (700 g) exist intracellularly and in bones.

- About 1% of total body phosphates exist extracellularly as HPO_4^{2-} and H_2PO_4- in a 4:1 ratio, with normal serum phosphate concentrations of 2.8 to 4.5 mg/dL.
- Less than 1% of total body phosphate is involved in constant bone turnover.
- Daily phosphate intake is approximately 1 to 1.5 g/d, where 60% to 80% is absorbed by the GI tract.
- Kidneys excrete most of dietary intake.
- Approximately 0.2 g is secreted into GI lumen daily.
- Physiologic roles of phosphate: bone mineralization, phospholipid bilayers, part of adenosine triphosphate (ATP) and DNA/RNA, glycolysis, cell function and signaling, unloading of O_2 via 2,3-bisphoglycerate

Phosphate Metabolism (Figure 3.5)

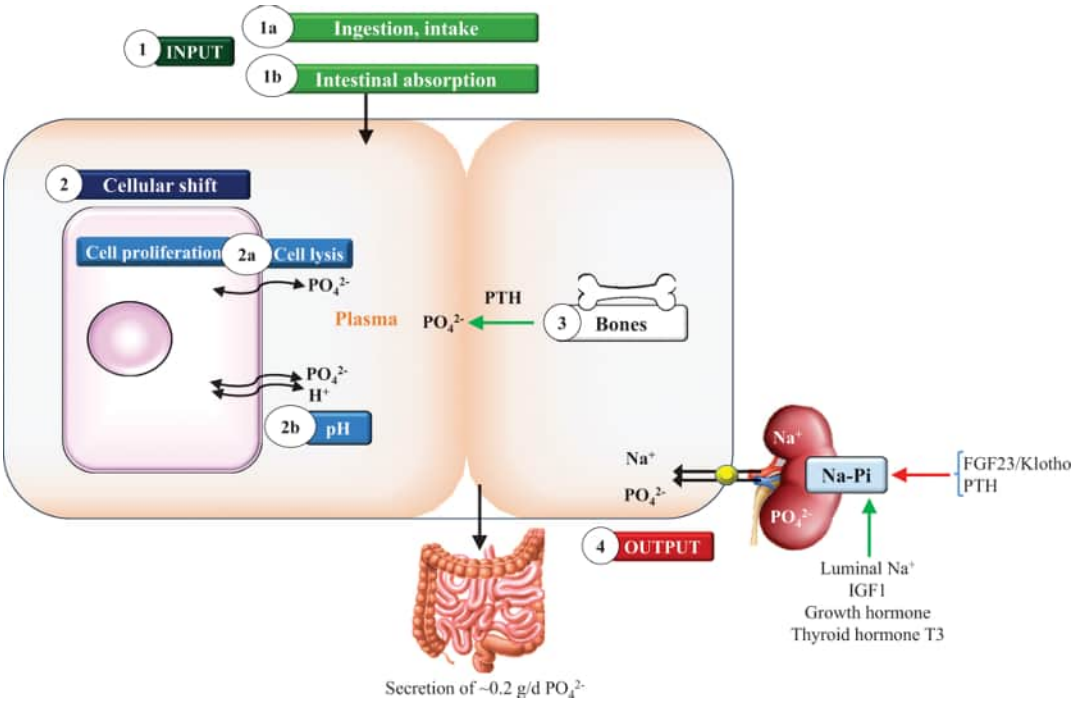


FIGURE 3.5 **Phosphate metabolism.** Plasma phosphate level is dependent on 1. input: 1a. ingestion, 1b. intestinal absorption; 2. cellular shift: 2a. cell proliferation increases cellular phosphate uptake while cell lysis increases extracellular phosphate shift, 2b. acid-base status: metabolic acidosis, that is, lactic acidosis or diabetic ketoacidosis, increases extracellular shift while acute respiratory

alkalosis increases intracellular shift; 3. bone formation increases phosphate uptake while bone lysis releases phosphate into plasma. PTH can stimulate bone resorption and release phosphate into plasma; and 4. Output: Sodium phosphate cotransporters (Na-Pi) in renal proximal tubules reabsorb filtered phosphate. Na-Pi, thus phosphate reabsorption, is inhibited by the FGF23-Klotho and PTH. The gut secretes approximately 0.2 g phosphate daily. Green arrow indicates positive effect. Red arrow indicates inhibitory effect. Bidirectional arrows indicate the direction of phosphate shift is conditional. See explanations for 2a and 2b.
Abbreviations: FGF23, fibroblast growth factor 23; IGF1, insulin-like growth factor 1; Na-Pi, sodium phosphate cotransporter; PTH, parathyroid hormone.

Phosphate homeostasis is maintained by intestinal absorption, cellular shifts, and renal excretion. It is thought that phosphate level can be sensed by multiple organs, all acting in concert to maintain phosphate homeostasis. Phosphate-sensing mechanism remains to be elucidated.

GI tract

Absorption occurs via both paracellular and transcellular pathways.

Paracellular absorption

Paracellular absorption is dependent on dietary intake and constitutively active.

- Mechanisms of paracellular absorption are not defined. However, reduced paracellular Pi absorption has been shown with the use of tenapanor, an NHE3 inhibitor.
- Dietary Pi sources:
  - Inorganic phosphate (Pi) from processed food with Pi-based additives (high bioavailability, ie, very easily absorbed)
  - Pi linked to organic molecules: Pi linked to dairy products or nonprocessed meats are cleaved by alkaline phosphatase at intestinal lumen prior to being absorbed.
  - Pi linked to phytic acid/phytate: Pi linked to phytates (eg, vegetables, fruits, corn, grains) are released as Pi by the intestinal enzyme phytase prior to being absorbed. Human phytase level is low, which explains low bioavailability of Pi from phytates.

Transcellular absorption

Transcellular absorption occurs via sodium phosphate (Na-Pi) cotransporters, type 2b in the small intestines (NPT2b), found mostly in

small intestines (duodenum and jejunum).

- NPT2b, the gene encoding Na-Pi 2b, is upregulated by dietary Pi intake and calcitriol and downregulated by inflammation.
- Niacin inhibits Na-Pi 2b and can be used to reduce GI Pi absorption.
- Deletion of NPT2b has no phosphate phenotype in humans. It is possible that paracellular absorption alone may be sufficient to maintain phosphate levels.

Cellular shifts

- Factors that increase cellular uptake: glucose/insulin infusion, parenteral hyperalimentation, refeeding syndrome, post-liver surgery, hyperventilation/(acute) respiratory alkalosis, hungry bone syndrome, salicylate poisoning
- Extracellular release: tissue injury/cell death, for example, rhabdomyolysis, tumor lysis, hemolysis, crush injury, hyperthermia, fulminant hepatitis, metabolic or respiratory acidosis

Renal excretion

- Phosphate is minimally protein-bound and freely filtered in the glomeruli.
- Total renal reabsorption is approximately 70% to 90%, which occurs predominantly in PT. Approximately 5% to 20% of the filtered phosphate load is excreted to maintain phosphate balance, that is, fractional excretion of phosphate ($FePO_4$) is 5% to 20%.

Proximal tubules

- Phosphate absorption is via Na-Pi 2a, 2c, and PiT-2 at brush borders of PT.
- Na-Pi 2a and 2c form a protein complex that is linked to the cytoskeleton. This protein complex is stabilized and regulated by NHERF1 (Na^+-H^+-exchanger regulatory factor 1).
- With phosphate loading, FGF23 and PTH downregulate Na-Pi 2a and 2c, thereby increasing phosphaturia.
- FGF23 requires the cofactor Klotho for optimal function. Mutations of either FGF23 or Klotho can lead to phosphaturia.

- Factors that reduce phosphaturia: insulin-like growth factor (IGF1), thyroid hormone T3, growth hormone
- In CKD, when GFR is reduced, each of the remnant nephrons will have to excrete more phosphate per filtered load to maintain balance. $FePO_4$ can exceed 50%.

Indices used to assess renal phosphate excretion

Fractional excretion of phosphate

$$FePO_4 = (UPO_4 \times S_{Cr}) / (SPO_4 \times U_{Cr})$$

where U_{PO4} = urine phosphate concentration, S_{Cr} = serum creatinine, S_{PO4} = serum phosphate concentration, and U_{Cr} = urine creatinine concentration.

Fractional tubular reabsorption of phosphate (TRP) = $1 - FePO_4$

- Since $FePO_4$ is normally less than 20% or 0.2, a fractional tubular reabsorption of PO_4 ($1 - FePO_4$) less than 0.8 suggests phosphaturia.
- Normal TRP ranges from 0.85 to 0.95.
- TRP should be measured in the second morning spot urine after an overnight fasting along with S_{PO4}. Fasting stimulates maximal tubular phosphate reabsorption. Morning collections minimize circadian and hormonal regulatory variations in PO_4 reabsorption.

Tubular maximum reabsorption of PO_4 per unit GFR (TmP/GFR) is the gold standard for evaluating phosphate disorders. TmP/GFR = $S_{PO4} - (U_{PO4}/U_{Cr}) \times S_{Cr}$. A low TmP/GFR ratio indicates renal PO_4 wasting. Reference range for adults is 2.60 to 3.80 mg/dL.

HYPERPHOSPHATEMIA

Background

- Hyperphosphatemia can arise from increased intestinal absorption, release from soft tissues, or reduced renal phosphate excretion.
- Hyperphosphatemia in the general population with normal kidney function is associated with increased risk for cardiovascular and

renal diseases and overall mortality.

Causes of Hyperphosphatemia

Common causes of hyperphosphatemia are summarized in **Figure 3.6**.

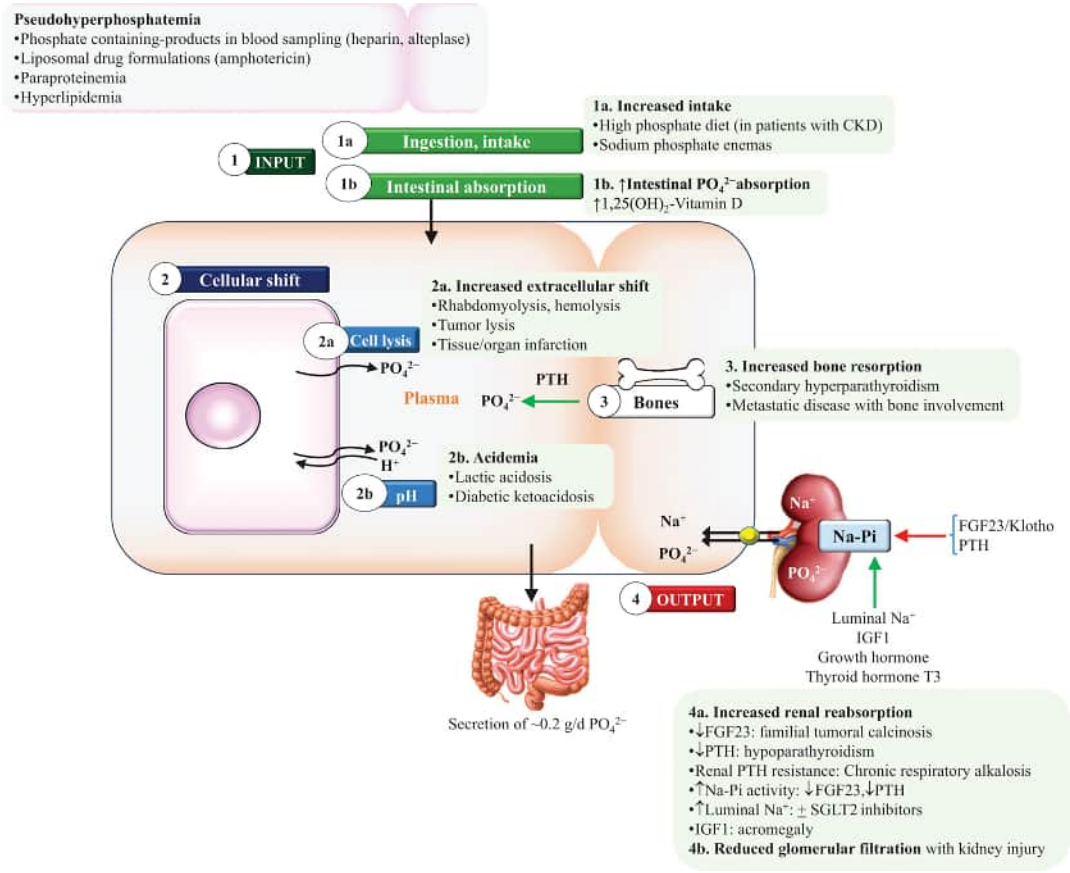


FIGURE 3.6 Etiologies of hyperphosphatemia.
Abbreviations: CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; IGF1, insulin-like growth factor 1; Na-Pi, sodium phosphate cotransporter-2; PTH, parathyroid hormone; SGLT2, sodium-glucose cotransporter type 2.

Pseudohyperphosphatemia

Heparin and alteplase-contaminated blood sampling: These solutions may contain phosphoric acid as a buffer solution.

Liposomal-coated drugs such as liposomal amphotericin: The phosphate hydrolyzed from liposomal phospholipid bilayer at the low pH used in the assay to measure serum phosphorus is falsely read as part of serum phosphate.

Paraproteinemia (eg, multiple myeloma, Waldenström macroglobulinemia, monoclonal gammopathy of undetermined significance)

- Precipitation of paraproteins and associated turbidity may interfere with light absorbance by ultraviolet spectrophotometry.
- Excess binding of phosphate to certain paraproteins
- Specific physiochemical characteristics of paraproteins per se may interfere with phosphate measurements.

Hyperlipidemia: presumed associated turbidity

Exogenous sources (usually in association with poor kidney function and excretion)

Ingestion: ingestion of phosphate salts, for example, accidental ingestion of phosphate-containing enemas. Of interest, data from the Veterans Affairs database revealed that the use of sodium phosphate enemas prior to colonoscopy increased the likelihood of having long-term eGFR decline compared with the use of polyethylene glycol (odds ratio 1.4).

NOTE

Phosphate-containing bowel preparation is not recommended in patients with GFR less than 60 mL/min/1.73 m^2 due to risk of acute phosphate nephropathy.

Calcitriol: Calcitriol increases GI absorption of phosphates.

Extracellular shift

Cell death, extracellular release of phosphate: rhabdomyolysis, crush injury, hemolysis, malignant hyperthermia, heavy tumor burden with necrotic cell death, tumor lysis syndrome, bowel infarction

Acid-base status

- Metabolic acidosis: lactic acidosis, diabetic ketoacidosis
- Chronic respiratory alkalosis (associated with prolonged hyperventilation) may lead to renal resistance to PTH,

hyperphosphatemia, hypocalcemia, and possibly reduced PTH secretion.

Increased bone resorption (in association with poor renal phosphate excretion)

- Secondary hyperparathyroidism (primary hyperparathyroidism is typically associated with hypophosphatemia)
- Metastatic disease with bone involvement

Reduced renal excretion

Reduced kidney function (typically with eGFR <25-30 mL/min/1.73 m^2)

Hypoparathyroidism (idiopathic, postsurgical, pseudohypoparathyroidism, PTH resistance, abnormal forms of plasma PTH)

Acromegaly

- Increased insulin-like growth factor-1 in acromegaly is thought to increase TRP via stimulation of Na-Pi cotransporters.
- Increased calcitriol with increased intestinal phosphate absorption may also be contributory.

Familial tumoral calcinosis

- Rare autosomal recessive disorder affecting Middle Eastern or African ancestries
- Thought to involve inactivating mutations of GALnt3, FGF23, or Klotho genes, all of which are necessary for optimal FGF23 activity. GALnt3 encodes glycosyltransferase, an enzyme necessary for posttranslational processing and stabilization of FGF23.
- The lack of active FGF23 (low FGF23) leads to:
  - Hyperphosphatemia
  - Loss of FGF23 inhibitory effect on 1,25 vitamin D synthesis → elevated $1,25(OH)_2D$ (increased GI calcium absorption) → reduced PTH → hypercalciuria
  - Ectopic calcifications due to combination of positive calcium balance and hyperphosphatemia

- Despite having ectopic calcifications, serum calcium tends to be normal due to opposing effects of $1,25(OH)_2D$ and PTH above.

Drug-induced

- Bisphosphonates may cause a transient rise in serum phosphate level due to increased renal tubular reabsorption. This effect, however, is normally overridden by the secondary increase in PTH induced by bisphosphonates. Sustained increase in serum phosphate may occur in patients with underlying hypoparathyroidism.
- SGLT2 inhibitors: It is presumed that the inhibition of sodium-glucose by the SGLT2 inhibitor increases luminal Na^+, thereby providing the electrochemical gradient favorable for sodium phosphate reabsorption via Na-Pi cotransporters. The resulting increased phosphate reabsorption leads to elevated serum phosphate levels, followed by increased FGF23 secretion → reduced $1,25(OH)_2D$ → increased PTH. The compensatory increase in FGF23 and PTH corrects the initial rise in serum phosphate but has been implicated in increased bone loss and fracture risks.

Clinical Significance of Hyperphosphatemia

- Soft tissue and vascular calcium phosphate depositions
- Hyperphosphatemia inhibits the conversion of 25-vitamin D to $1,25(OH)_2D$ (calcitriol).
- Data from the Third National Health and Nutrition Examination Survey (1988-1994) revealed that fasting, but NOT nonfasting, serum phosphorus levels were associated with increased mortality.

Management of Hyperphosphatemia

Dietary restriction: Avoid food with preservatives.
Fluid resuscitation to ensure good renal excretion
Use of phosphate binders with meals to reduce GI absorption of dietary phosphates (see "Secondary hyperparathyroidism" section)
Administration of intravenous dextrose and insulin to increase intracellular phosphate shift if clinically indicated

HYPOPHOSPHATEMIA

Hypophosphatemia can arise from reduced intake or intestinal absorption or both, increased cellular uptake, or increased renal phosphate excretion.

Clinical Manifestations of Hypophosphatemia

- Muscle weakness, rhabdomyolysis, respiratory arrest due to weak diaphragm, cardiomyopathy
- Metabolic encephalopathy, neuropathies, tremors, seizures, coma
- Hemolysis, white blood cell dysfunction, impaired chemotaxis and phagocytosis, thus increased risk for infections
- Insulin resistance (glycolysis requires phosphate)

Causes of Hypophosphatemia

Common causes of hypophosphatemia are summarized in **Figure 3.7.**

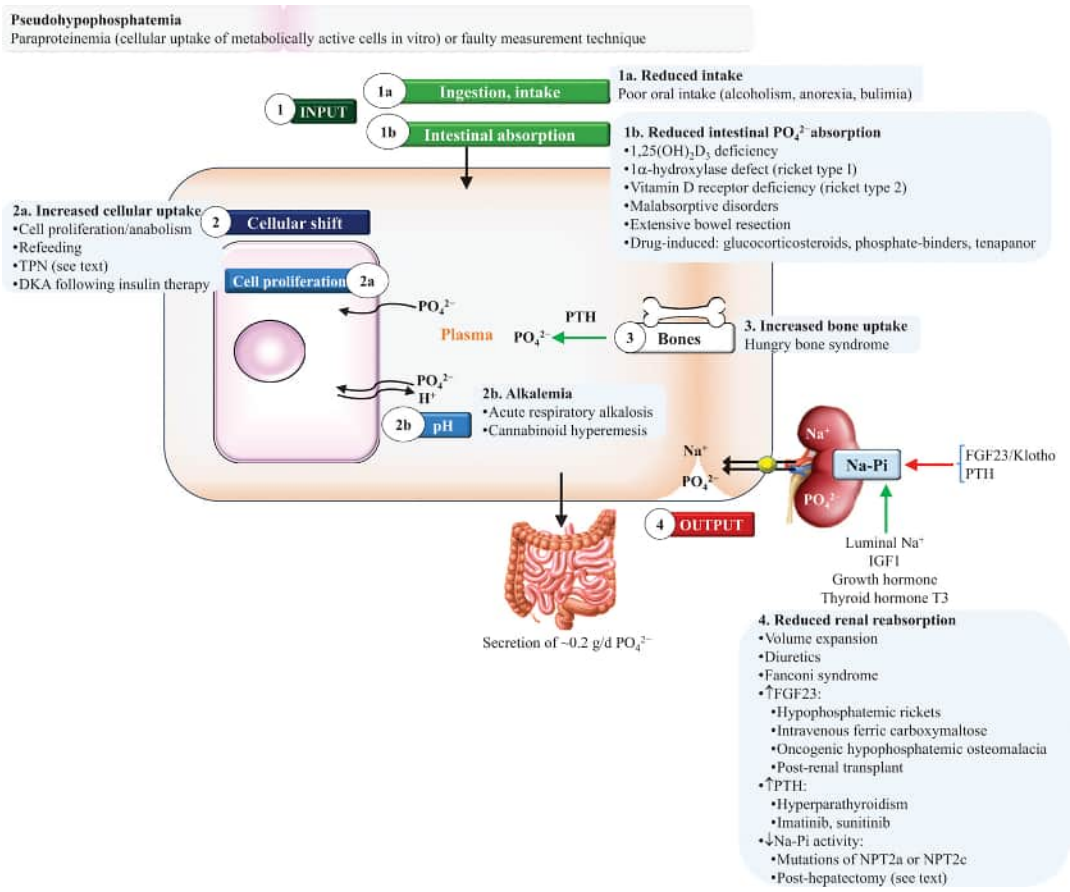


FIGURE 3.7 Etiologies of hypophosphatemia.
Abbreviations: DKA, diabetic ketoacidosis; FGF23, fibroblast growth factor 23; IGF1, insulin-like growth factor 1; Na-Pi, sodium phosphate cotransporter-2; NPT2a, gene encoding Na-Pi-2a; NPT2c, gene encoding Na-Pi-2c; PTH, parathyroid hormone; TPN, total parenteral nutrition.

Pseudohypophosphatemia

Paraproteinemia interference with laboratory assays—If this is suspected, blood samples should be deproteinized, ultra-filtrated or diluted prior to analysis or run on a different automated assay known to have less interference by paraproteins.

Reduced intake

Hypophosphatemia may be seen in patients with alcohol abuse or eating disorders (anorexia, bulimia) or in patients who are old, with physical debilitation, or with low income and with poor access to high phosphate-containing food.

Reduced intestinal absorption due to vitamin D deficiency

Vitamin D–dependent rickets type 1: defect in renal 1α-hydroxylase

- Laboratory findings: low $1,25(OH)_2D$, hypocalcemia, secondary hyperparathyroidism (sHPT), hypophosphatemia
- Around 50% of patients may have alopecia.
- Treatment: low-dose calcitriol

Vitamin D–dependent rickets type 2: VDR deficiency

- Laboratory findings: high $1,25(OH)_2D$ level
- Treatment: high-dose calcitriol

Malabsorptive GI disorders, extensive bowel resection

Tenapanor (FDA-approved for irritable bowel syndrome)**:** A selective inhibitor of intestinal NHE3 transporter that decreases paracellular PO_4 absorption in the intestine, thereby decreasing serum phosphorus levels. It is being evaluated for use in patients with CKD-associated hyperphosphatemia.

Cellular shift

Acute respiratory alkalosis (hyperventilation)

- Hyperventilation leads to extracellular CO_2 diffusion, thereby increasing intracellular pH. The increased intracellular pH promotes glycolysis and downstream ATP production. ATP synthesis requires rapid cellular phosphate uptake, hence extracellular hypophosphatemia.
- Cannabinoid hyperemesis syndrome may present with hypophosphatemia. Hyperventilation-induced cellular uptake of phosphate is thought to be contributory.

NOTE

- Acute metabolic alkalosis does NOT cause hypophosphatemia because bicarbonate cannot freely cross cell membranes to cause a rapid rise in intracellular pH.
- Chronic respiratory alkalosis is associated with HYPERphosphatemia due to renal resistance to PTH with/without reduced PTH secretion.

Refeeding syndrome
Total parenteral nutrition (TPN) due to low phosphate content or endogenous insulin-mediated intracellular phosphate shift following TPN infusion
Insulin administration in the treatment of diabetic ketoacidosis

Increased renal excretion

Volume expansion
FGF23 gain-of-function mutations
FGF23 gain-of-function mutations can lead to reduced expression of Na-Pi cotransporters. Affected individuals may present with various skeletal deformities.

- Autosomal dominant hypophosphatemic rickets:
  - Mutation in FGF23 that renders FGF23 resistant to proteolysis
  - Associated skeletal abnormalities: bowing of long bones and widening of costochondral joints
- Autosomal recessive hypophosphatemic rickets: Mutations in DMP1 can lead to increased FGF23 levels. DMP1 is a gene encoding the dentin matrix protein 1, a molecule thought to normally suppress bone secretion of FGF23.
- X-linked hypophosphatemic rickets:
  - Mutations of the PHEX gene encoding the phosphate regulating endopeptidase (on X chromosome). PHEX is thought to play a role in the proteolysis of FGF23.
  - Associated skeletal deformities: short stature, osteomalacia

Drug-induced increase in FGF23
Intravenous ferric carboxymaltose administration in patients *with iron deficiency* can lead to severe hypophosphatemia (even to level <1 mg/dL). The mechanism is not clear but thought to be due to increased FGF23 levels. It has been suggested that the drug can inhibit the cleavage and inactivation of FGF23 within osteocytes, resulting in increased levels of active FGF23, phosphaturia, hypophosphatemia, and decreased $1,25(OH)_2D$ level. Hypophosphatemia typically nadirs at approximately 2 weeks and resolves within 3 months following a single intravenous dose but may last over a year with repeated doses.

Intrinsic renal defect leading to reduced renal phosphate reabsorption

- Fanconi syndrome
- Mutation of NPT2a: autosomal recessive Fanconi syndrome with associated hypophosphatemic rickets and kidney failure
- Mutation of NPT2c: hereditary hypophosphatemia with rickets and hypercalciuria (HHRH). Hypophosphatemia associated with mutations of NPT2a and 2b stimulates calcitriol synthesis, thus hypercalcemia and hypercalciuria, while inhibiting FGF23 and PTH.

Tumor-induced osteomalacia, aka oncogenic hypophosphatemic osteomalacia

- Mostly associated with benign mesenchymal tumors of mixed connective tissue type (eg, hemangiopericytoma, fibroma, angiosarcoma, metastatic prostate carcinoma)
- Malignant tissue-secretion of phosphatonins (ie, FGF23 and other phosphaturic factors)
- Clinical manifestations:
  - Affected individuals present with impaired bone mineralization and hypophosphatemia caused by reduced renal phosphate reabsorption.
  - Bone pain, muscle weakness, difficulty walking, pathologic fractures, height loss
- Laboratory findings:
  - Elevated FGF23, hypophosphatemia, low $1,25(OH)_2D$, elevated PTH, normal to low serum calcium
  - Calcitriol is inappropriately low to normal in this condition due to reduced 1α-hydroxylase activity with increased FGF23 levels.
  - PTH may be elevated due to low $1,25(OH)_2D$ levels or excessive phosphate replacement.
  - Alkaline phosphatase levels are often elevated.
- Diagnosis: clinical manifestations above, markedly elevated FGF23, hypophosphatemia, increased serum alkaline phosphatase, reduced TmP/GFR

Post-renal transplant hypophosphatemia (also see **Chapter 9: Kidney Transplantation**)

- Persistent sHPT in new functioning allograft
- Persistently high circulating levels of FGF23, although this is more commonly seen in patients with markedly elevated pretransplant FGF23 levels
- Note, however, that persistent hypophosphatemia beyond 1-year posttransplant has been attributed to persistent hyperparathyroidism rather than increased FGF23 levels.

Others

- Drugs: glucocorticosteroids, phosphate binders, diuretics, tyrosine kinase inhibitors (eg, imatinib, sunitinib are associated with hyperparathyroidism presumably secondary to skeletal resistance, normal to high serum calcium levels, hypophosphatemia). Tyrosine kinase inhibitors are used in the treatment of various malignancies, including pancreatic neuroendocrine tumors, GI stromal tumors, and advanced renal cell carcinoma, and Philadelphia chromosome-positive chronic myelogenous leukemia.
- Alcoholism: malnutrition, hypomagnesemia-associated renal phosphate wasting, intracellular shift due to hyperventilation or glucose infusion
- Hungry bone syndrome
- Hypophosphatemia following hepatectomy: This is thought to be due to increased proximal tubular expression of nicotinamide phosphoribosyl-transferase (Nampt), a protein associated with reduced renal expression of Na-Pi cotransporters.
- Electrolyte disturbances: hypokalemia and metabolic acidosis (reduced Na-Pi 2a activity)

Management of Hypophosphatemia

Phosphate supplementation

- Estimating phosphate deficit (ie, repletion dose):
- Phosphate dose (mmol) = 0.5 × body weight (kg) × (1.25 – [serum phosphate mmol/L])

Anti-FGF23 antibody: Burosumab was FDA-approved in 2018 for the treatment of:

- X-linked hypophosphatemia (XLH) in patients above 6 months of age
- Hypophosphatemia associated with tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients 2 years of age and above.

SECONDARY HYPERPARATHYROIDISM

Clinical Implications and Complications Associated With sHPT

- DOPPS investigators reported that PTH level inversely correlates with weight loss and U-shape pattern with mortality. Patients with PTH level 600 pg/mL and above had the greatest mortality risk.
- Renal osteodystrophy with increased risk of fractures: osteomalacia, osteopenia, adynamic bone disease, mixed bone disease
- Calcific uremic arteriolopathy, aka calciphylaxis
- Accelerated atherosclerosis
- Refractory anemia
- Tertiary hyperparathyroidism

Diagnosis

sHPT may be diagnosed in patients with CKD and is characterized by elevated serum PTH levels, normal to high serum phosphate, and normal to low serum calcium.

Pathogenesis

The pathogenesis of CKD-associated sHPT involves multiple factors, as illustrated in **Figure 3.8**.

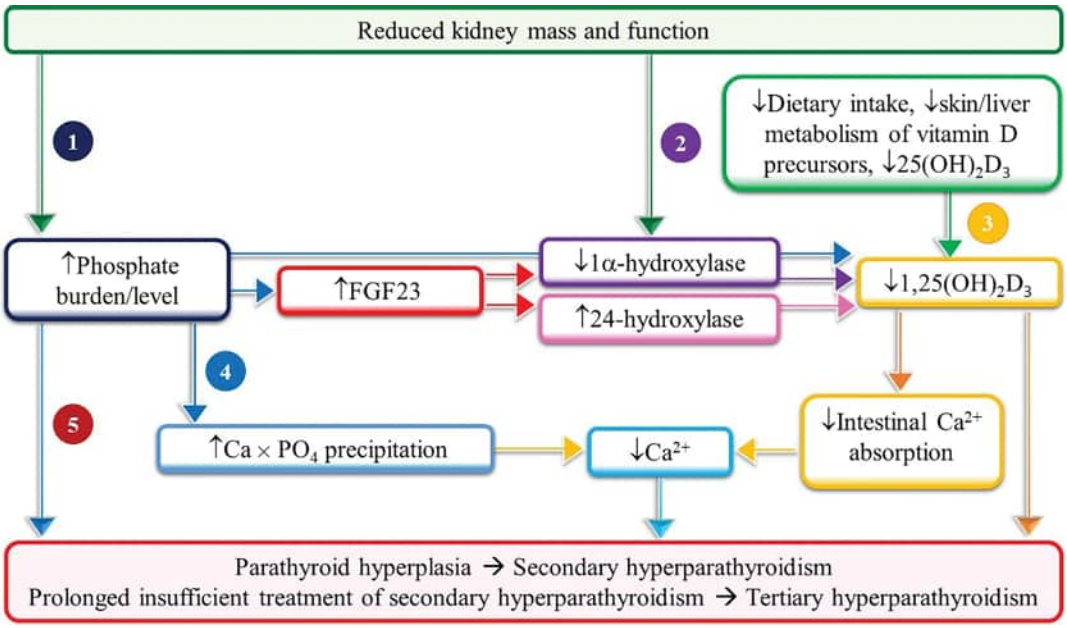


FIGURE 3.8 Pathogenesis of secondary and tertiary hyperparathyroidism in patients with chronic kidney disease. 1. Reduced kidney function leads to increased phosphate burden, which leads to increased FGF23 levels and subsequent reduction in $1,25(OH)_2D_3$ synthesis and plasma calcium levels. Both reduced plasma $1,25(OH)_2D_3$ and calcium levels stimulate parathyroid hyperplasia and development of secondary hyperparathyroidism. 2. Severely reduced kidney function per se may further reduce the availability of 1α-hydroxylase and contributes to reduced $1,25(OH)_2D_3$. 3. Poor dietary intake and reduced skin and liver metabolism of vitamin D precursors may also play a role in reducing $1,25(OH)_2D_3$ levels. 4. Hyperphosphatemia may precipitate with calcium, thereby lowering plasma calcium level. The latter can stimulate parathyroid proliferation. 5. Hyperphosphatemia may also directly stimulate parathyroid glands. Prolonged untreated secondary hyperparathyroidism can result in tertiary hyperparathyroidism.
Abbreviations: $1,25(OH)_2D_3$, $1,25(OH)_2$–vitamin $D_{3\ \text{aka calcitriol}}$; FGF23, fibroblast growth factor-23; PTH, parathyroid hormone.

Reduced kidney mass and function

Reduced kidney mass and function reduces glomerular filtration and lead to phosphate retention.

Phosphate retention

- Stimulates parathyroid gland (via CaSR) to increase PTH secretion and parathyroid cell growth
- Increases parathyroid cell resistance to calcitriol

- Induces skeletal resistance to PTH
- Reduces calcitriol synthesis (feedback loop: calcitriol increases phosphate level while high phosphate level reduces calcitriol synthesis)
- Stimulates FGF23 synthesis

Increased FGF23

Induces phosphaturia via suppression of Na-Pi 2a and 2c expressions in proximal tubular brush border. FGF23 has low affinity for its receptor (FGFR1) and requires the cofactor Klotho to effectively bind and activate the receptor. Klotho expression is reduced early in CKD. This is thought to be the reason for reduced phosphaturia in CKD. Reduction of Klotho has been implicated in greater CKD progression.

Reduces $1,25(OH)_2D$ synthesis by inhibiting 1α-hydroxylase and stimulating 24-hydroxylase. Reduced kidney mass also contributes to reduced 1α-hydroxylase activity.

Inhibits parathyroid gland via

- Reducing PTH synthesis and secretion and PTH proliferation
- Increasing expression of CaSR and VDR

Reduced $1,25(OH)_2D$ level

- Reduces intestinal absorption of calcium
- Reduces repression of PTH gene transcription and parathyroid cell proliferation
- Reduces expression of parathyroid VDR and CaSR
- Increases set-point for calcium-regulated PTH secretion, all leading to hyperparathyroidism

Other factors contributing to CKD-associated sHPT

- Patients with kidney disease may also have reduced skin conversion of 7-dehydrocholesterol to cholecalciferol and liver hydroxylation of cholecalciferol to $1,25(OH)_2D$.
- Hypocalcemia unrelated to vitamin D deficiency

- Poor dietary intake, malnutrition
- Systemic $CaPO_4$ precipitation

NOTE

NOTES regarding FGF23 in CKD

- FGF23 level is increased early in CKD, even before the rise in PTH levels. The elevated FGF23 level is thought to be associated with the increase phosphate "burden" alone and not necessarily high serum phosphate levels.
- FGF23 is an independent predictor of mortality, progression of kidney disease, left ventricular hypertrophy, vascular dysfunction, and kidney transplant outcomes.
- FGF23 levels may remain increased post-kidney transplant (typically within the first year only) with resultant hypophosphatemia and relative $1,25(OH)_2D$ deficiency.

Management of Secondary Hyperparathyroidism

See **Table 3.3**, for a summary of 2017 KDIGO chronic kidney disease–mineral and bone disorder (CKD-MBD) guidelines.

Table 3.3 Summary of KDIGO 2017 CKD-MBD guidelines

CKD-MBD		G3a-5	Dialysis	Kidney transplant
Bone health	BMD testing	Patients with evidence of CKD-MBD and/or osteoporosis risks, **BMD testing is suggested** if it will impact treatment decisions.		BMD testing is suggested in patients with osteoporotic risks.
	Bone biopsy	Performing a bone biopsy is reasonable if type of renal osteodystrophy will impact treatment decisions. In patients with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, treatment choices accounting for biochemical abnormalities and progression of CKD with consideration of a bone biopsy is suggested.		It is reasonable to consider a bone biopsy to guide treatment. In patients with low BMD and eGFR >30 mL/min/1.73 m^2 in the first 12 mo, treatment consideration with vitamin D, calcitriol/alfacalcidol, and/or

CKD-MBD		G3a-5	Dialysis	Kidney transplant
				antiresorptive agents is suggested.
CKD-MBD biochemical profile • Treatment of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together.	Calcium	[a]**Avoiding hypercalcemia** is suggested in adults. Mild and asymptomatic hypocalcemia, particularly in the setting of calcimimetic use, may be tolerated to avoid inappropriate calcium loading.		
			Suggested dialysate [Ca^{2+}]: 1.25-1.50 mmol/L	
	Phosphate	**Lowering phosphate levels toward normal range** is suggested. • [b]Phosphate-lowering treatment should be based on progressively or persistently elevated phosphate level. • [c]Limiting dietary phosphate intake is suggested. • [a]Restricting calcium-based phosphate binders is suggested.		
	PTH	Optimal PTH level is not known. Evaluation for modifiable factors (eg, hyperphosphatemia, hypocalcemia, hypovitaminosis D) in patients with **persistently or progressively elevated iPTH** is suggested.		
	Vitamin D	• Measurements of 25(OH)D (calcidiol) level are suggested with repeated testing done as clinically indicated. • Treatment of vitamin D deficiency/insufficiency is similar to recommendations for the general population.		
		[d]**Routine use of calcitriol/active vitamin D analogs is not suggested** but reasonable for G4-G5 with severe	[e]In patients with CKD-G5D requiring PTH-lowering	

CKD-MBD		G3a-5	Dialysis	Kidney transplant
		and progressive hyperparathyroidism.	therapy, vitamin D analog, calcitriol, calcimimetic, or combination is suggested.	

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; G5D, stage 5 with dialysis; iPTH, intact parathyroid hormone; MBD, mineral and bone disorder; PTH, parathyroid hormone.

CKD G3a-5D

- Measurements of 25(OH)D (calcidiol) levels are suggested with repeated testing as needed. Replacement follows recommendations for the general population.
- For progressively rising PTH levels, evaluation for hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency should be done.
- Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together.

Avoiding hypercalcemia, rather than maintaining serum calcium in the normal range, is suggested. Higher calcium concentrations have been linked to increased mortality and nonfatal cardiovascular events.

Phosphate-lowering therapy

- Lowering elevated phosphate levels *toward normal range* (rather than maintaining serum phosphate in the normal range) is suggested.
- Phosphate-lowering therapy includes binders, diet, and/or dialysis (rather than just using phosphate-binding agents).
- Phosphate-lowering therapy should be based on *progressively or persistently elevated serum phosphate* (rather than a single value).

Considerations for dietary phosphate restriction

- Fresh homemade foods without inorganic Pi-containing additives are preferred.
- Plant-based phosphate sources have lower bioavailability compared with phosphates from animal sources, 20% to 50% in the former versus 40% to 60% in the latter.
- Care must be taken to avoid malnutrition.

Bone health: Bone mineral density testing (eg, dual-energy x-ray absorptiometry [DEXA]) *is suggested* to assess fracture risk if results will impact treatment decisions.

CKD G3a-5 (without dialysis)

Routine *use of calcitriol and vitamin D analogs is not suggested* but reasonable for G4-G5 with severe and progressive hyperparathyroidism. Randomized controlled trials of vitamin D analogs demonstrated increased hypercalcemia risks and lack of clinically relevant benefits.

The use of calcimimetics is not indicated for patients with CKD not on dialysis due to lack of long-term safety and efficacy, particularly regarding risks for hypocalcemia and phosphate retention. Patients receiving dialysis generally have lower risks for hypocalcemia due to their relatively higher baseline calcium levels. In patients with non-anuric kidney function who are in the predialysis stage, calcimimetics may increase phosphate retention by inhibiting PTH and its phosphaturic effect. This reduced phosphaturic effect is not an added concern for patients receiving dialysis who are anuric.

CKD G5D

- In patients requiring PTH-lowering therapy, suggested therapeutic options include calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs. *All agents are considered acceptable first-line options*.
- Maintaining PTH within the range of 2 to 9 times of upper normal limit is suggested.

Phosphate control

Dietary phosphate restriction (typically 1,000 mg/d)

- Phosphate source from plants have lower bioavailability compared to meat source, which has lower bioavailability than inorganic phosphate from food additives.
- Excess dietary phosphate ingestion increases the formation of calciproteins, which are colloidal calcium phosphate complexed to various circulating proteins. Calciproteins in renal tubular fluid can damage epithelial cells and are thought to promote CKD progression.

Inhibitors of intestinal phosphate transporters

- COMBINE trial: The use of nicotinamide 750 mg bid (intestinal Na-Pi 2b inhibitor) and/or lanthanum carbonate 1,000 mg tid (non–calcium phosphate binder) in CKD stages 3b/4 did not significantly lower serum phosphate or FGF23 over 12 months.
- AMPLIFY trial (phase 3): The addition of tenapanor, an NHE3 inhibitor that decreases GI paracellular phosphate absorption, to hemodialysis for patients with serum phosphate levels between 5.5 and 10 mg/dL, despite being on traditional phosphate binder therapy, was shown to lower serum phosphate by 0.84 mg/dL and reduce FGF23 by 24% (compared to 0.19 mg/dL and 6.9%, respectively, in placebo group). The main adverse effect of tenapanor was diarrhea.

Phosphate binders

- Commonly used agents in the United States and their notable and important clinical findings are reviewed in **Table 3.4**.
- The use of more than 1.5 g/d of calcium-based phosphate binders can lead to positive calcium balance and is not recommended.
- Iron-based phosphate binders (eg, sucroferric oxyhydroxide, ferric citrate) concurrently treat iron deficiency and lower FGF23 (FGF23 is a hormone-linked to increased cardiovascular morbidity and mortality).
- IMPROVE-CKD trial: Lanthanum carbonate had no significant effect on serum phosphate, PTH, FGF23, 24-hour urine phosphate excretion, or vascular stiffness or calcification in CKD 3b/4.

FYI

Despite strong evidence indicating the association between hyperphosphatemia and multiple CKD-related comorbidities, data demonstrating clinically relevant beneficial effects of phosphate-lowering therapy are lacking. A 2022 meta-analysis involving 20 randomized controlled trials of at least 3 months duration involving 2,500 participants concluded that although non-calcium-based phosphate-lowering therapy-reduced serum phosphate and urinary phosphate excretion, the effects on clinical outcomes and intermediate cardiovascular end points were unclear.

The HiLo and PHOSPHATE trials are prospective, multicenter, randomized clinical trials aimed to determine how targeting a high serum phosphate versus a lower serum phosphate alters a composite outcome of all-cause mortality or hospitalization in patients undergoing dialysis. Results are pending at the time of this writing.

Table 3.4 Characteristics of commonly used phosphate-binding agents used in the United States

Phosphate binders	Comments
Calcium acetate Calcium carbonate	• Elemental calcium content: 400 mg/g of calcium carbonate; 169 mg/667 mg of calcium acetate • Efficacy of calcium carbonate is reduced with the use of PPI or H2 blockers. • Vascular and coronary artery calcification has been shown to be greater compared to non-calcium-based agents such as sevelamer and lanthanum carbonate.
Sevelamer	• Interferes with GI absorption of active vitamin D, vitamin K, and levothyroxine • Reduces serum C-reactive protein, glycated hemoglobin, total and LDL cholesterols • No effect on FGF23, Klotho, intact PTH, or vitamin D levels • May crystallize in gut and leads to gastrointestinal mucosal injury
Lanthanum carbonate	• Although lanthanum can accumulate in various tissues including bones, data to date have not shown evidence for liver damage or increased bone fractures. • May crystallize in gut and leads to gastrointestinal mucosal injury • See text regarding lanthanum use in COMBINE and IMPROVE-CKD trials
Ferric citrate	Reduces FGF23 levels and increases hemoglobin

Phosphate binders	Comments
Sucroferric oxyhydroxide	• Reduces FGF23 levels • Reduces erythropoiesis stimulating agent and intravenous iron dose/requirement

Abbreviations: CKD, chronic kidney disease; FGF23, fibroblast growth factor-23; GI, gastrointestinal tract; LDL, low-density lipoprotein; PPI, proton pump inhibitors; PTH, parathyroid hormone.

Dialysis removal

- Hemodialysis removes approximately 800 mg of phosphorus per treatment.
- Peritoneal dialysis removes approximately 300 mg of phosphorus per treatment.
- Since phosphorus is predominantly intracellular, there is a post-dialysis rebound phenomenon due to extracellular shift.
- Prolonged and frequent dialysis (ie, nocturnal or daily hemodialysis) are superior in phosphorus removal than conventional hemodialysis. Increasing blood flow rate in hemodialysis is not effective in increasing phosphorus removal.

Vitamin D (cholecalciferol) supplementation

- "Vitamin D" refers to inert vitamin D (eg, cholecalciferol) prior to hydroxylation at carbons 1 and 25 to become the active $1,25(OH)_2D$.
- The prevalence of vitamin D deficiency is high among patients with CKD, up to 97% in those requiring hemodialysis. 25(OH)D level is routinely measured for vitamin D adequacy because hepatic hydroxylation at the 25th carbon occurs readily without any regulation.

Factors associated vitamin D deficiency in CKD

- Low sunlight exposure
- Uremia-associated blunting of the response of plasma vitamin D to UVB irradiation
- Uremia-associated skin hyperpigmentation and reduced UVB exposure

- Urinary loss of vitamin D-binding protein-vitamin D complexes due to proteinuria and reduced proximal tubular reabsorption
- Loss of vitamin D-binding protein-vitamin D complexes in peritoneal dialysate in patients receiving peritoneal dialysis
- Poor nutrition

Rationale for (inert) vitamin D supplementation

- Potential nonskeletal benefits: endothelial function, immunity, anti-inflammatory effect, regulation of the renin-angiotensin-aldosterone system, cardiac function/ventricular mass, response to erythropoietin stimulating agents, malignancy
- KDIGO suggests a dose of 1,000 to 2,000 IU/d of vitamin D3, with acknowledgment that a more aggressive therapeutic plan may be required.
- Ergocalciferol (D2) versus cholecalciferol (D3):
  - D2 is found in vegetables (eg, mushrooms) and "vitamin D-fortified" foods.
  - D3 is found in animal-based foods (eg, fish, meat, egg, dairy) or cutaneous conversion of 7-dehydroxycholesterol by UV sunlight in human.
  - Both ergocalciferol and cholecalciferol require hydroxylation at carbons 1 and 25 to become active $1,25(OH)_2D$.
- Suggested advantages of D3 over D2:
  - D3 may have greater affinity for 25-hydroxylase, hence better conversion to 25(OH)D.
  - D3 may have greater affinity for VDR.
  - D2 has been suggested to have lower affinity for vitamin D-binding protein compared with D3, hence higher systemic clearance and lower half-life compared to D3.
  - The use of either D2 or D3 may be based on potential benefits of D3 (discussed earlier) or local resources and/or patients' preference (ie, vegans may prefer D2).
- Rationale for concurrent use of vitamin D with calcitriol or active vitamin D analogs in advanced CKD:

- Vitamin D supplementation improves CKD-MBD, but may be insufficient to reduce PTH levels, particularly in later CKD stages G4 and G5. In advanced CKD, D2 or D3 may only be converted to 25(OH)D (calcidiol) but not to $1,25(OH)_2D$ (calcitriol). While calcidiol can bind to VDR to exert intended physiologic effects, its affinity is 100 times less than that of calcitriol.
- Low calcidiol levels are associated with increased mortality in patients undergoing hemodialysis.

Use of active vitamin D, aka VDRA

- VDRA formulations used in the United States: calcitriol: $1,25(OH)_2D_3$, doxercalciferol: $1\alpha\text{-}(OH)D_2$ (needs to be converted to $1,25(OH)_2D_2$ in liver), and paricalcitol: $19\text{-nor-}1\alpha,25(OH)_2D_2$
- Comparative clinical effects of commercially available VDRA:
  - Both doxercalciferol and paricalcitol are thought to confer lower rates of hypercalcemia and hyperphosphatemia compared to calcitriol. However, a 2017 meta-analysis comparing paricalcitol with other VDRA found no significant differences in the incidence of hypercalcemia or hyperphosphatemia.
  - Observational studies revealed that the use of parenteral non-calcitriol VDRA in patients undergoing dialysis is associated with decreased risk of hospitalization and mortality.
  - The use of parenteral paricalcitol is associated with improved survival compared to calcitriol.
- VDRA use is associated with increased FGF23 levels, an independent predictor of mortality among patients with CKD. Regardless, there have been no studies to date that have reported an association of VDRA use with increased mortality.
- Doxercalciferol 1(OH)-vitamin D needs to be hydroxylated at the 25 position to 1,25(OH)2D in the liver before it becomes an active vitamin D. Thus, the use of doxercalciferol may not be optimally effective in patients with advanced liver disease.

NOTE

Prior to any VDRA supplementation, serum phosphate levels should be reduced to below 5.5 mg/dL, because VDRA does increase GI absorption of phosphate and may worsen existing hyperphosphatemia.

Calcimimetics

Calcimimetics available in the United States: cinacalcet and etelcalcetide

Cinacalcet (30-180 mg/d)

- Mechanism of action: Cinacalcet acts on CaSR as a positive allosteric modulator to increase cellular sensitivity to extracellular calcium, thereby inhibiting parathyroid gland.
- Indications: Treatment of sHPT in adult patients with CKD G5D, parathyroid carcinoma, and pHPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are nonsurgical candidates.
- Adverse effects: hypocalcemia, upper GI bleeding, hypotension with/without worsening heart failure and/or arrhythmias, adynamic bone disease, chondrocalcinosis pyrophosphate (acute pseudogout)
- Cinacalcet-induced hypocalcemia:
  - Risk factors: high PTH and alkaline phosphatase, low serum calcium
  - Hypocalcemia is thought to be equivalent to post-parathyroidectomy hungry bone syndrome, albeit a milder form. This is predominantly asymptomatic with high likelihood for spontaneous recovery.
  - Therapy may not be necessary unless hypocalcemia is severe and symptomatic.

FYI

Prescribing information for use in CKD G5D: 1. Monitor serum calcium monthly-once maintenance dose has achieved. 2. For serum calcium between 7.5 and 8.4 mg/dL or symptomatic, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. 3. If level falls below 7.5 mg/dL or if symptomatic despite being on optimal dose of vitamin D, withhold cinacalcet until serum calcium reaches 8.0 mg/dL and/or resolution of symptomatic hypocalcemia. Re-initiation of cinacalcet should be done at a lower dose than previous dose.

- Effective in controlling difficult-to-treat secondary hyperparathyroidism in both patients on hemodialysis and those on peritoneal dialysis
- Cinacalcet has been shown to reduce FGF23, whereas VDRA increases FGF23 levels.

FYI

Cinacalcet effects on morbidity and mortality:

- Post hoc analysis of four randomized controlled trials, n = 1,184, with follow-up at 6 to 12 months revealed a reduction in risk of parathyroidectomy, fractures, and hospitalization.
- Effect of Cinacalcet Hydrochloride therapy to Lower Cardiovascular Events (EVOLVE) trial also suggested reduction in rate of clinical fracture with cinacalcet among patients with sHPT.
- Cinacalcet may reduce vascular calcification progression compared to VDRA therapy alone (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low-Dose Vitamin D on Vascular Calcification in Subjects with CKD) study.
- Cinacalcet has been suggested to reduce the incidence of calcific uremic arteriolopathy.
- Mortality data are conflicting. EVOLVE trial suggested a potential benefit of cinacalcet in risk reduction for death and cardiovascular outcomes. Cochrane analysis revealed no survival benefit.

Etelcalcetide (intravenous)

- Half-life of etelcalcetide is more than 7 days compared to 30 to 40 hours for cinacalcet.
- Indication: treatment of sHPT in adults with CKD on hemodialysis
- Mechanism of action: Etelcalcetide acts as a direct CaSR agonist. Unlike cinacalcet, whose action is to change the conformation of CaSR to better sense calcium, etelcalcetide directly activates CaSR in the absence of calcium.
- Hypocalcemia: Etelcalcetide plus VDRA combination has been shown to reduce risk of hypocalcemia better than etelcalcetide plus calcium-based phosphate binders.
- Phosphate toxicity: Compared with VDRA, etelcalcetide has been shown to have a salutary effect on phosphate toxicity as measured by reduced formation of calciproteins, which are calcium phosphate crystals thought to promote vascular calcifications.

- In a randomized trial involving patients undergoing hemodialysis, etelcalcetide reduced FGF23 and left ventricular mass index (LVMI), while alfacalcidiol increased both.
- Etelcalcetide may induce a greater FGF23 and PTH-lowering effect compared with cinacalcet. Whether this effect translates to improved survival compared with cinacalcet remains to be proven.

Combined VDRA and calcimimetics

- Both VDRA and calcimimetics reduce osteoclast differentiation, although the former may oversuppress osteoclasts compared to calcimimetics.
- Calcimimetics have anabolic effects on osteoblasts, but not apparent with VDRA.
- Combined low-dose VDRA and calcimimetics may better preserve bone health than either agent alone.

Management of hypocalcemia in patients with CKD

- KDIGO suggests that a daily intake of 1,000 mg elemental calcium provides neutral calcium balance in patients with CKD stage 3 or 4.
- Calcium supplement should not exceed 1,000 mg/d.
- For patients undergoing hemodialysis, KDIGO 2017 suggests the use of dialysate calcium concentration between 1.25 and 1.50 mmol/L or 2.5 and 3.0 mEq/L.
- Patients with CKD stage 3 or 4 can develop positive calcium balance when consuming dietary calcium 2,000 mg/d or more or receiving calcium carbonate containing 1,500 mg/d or more of elemental calcium. Positive calcium balance may promote accelerated vascular calcifications.

Parathyroidectomy (PTX) in patients with CKD and sHPT (Table 3.5)

Table 3.5 Indications for parathyroidectomy in patients with CKD and secondary hyperparathyroidism

Patients who have undergone non-renal transplants	Patients who have received renal transplants

• Elevated intact PTH levels >800 pg/mL that are refractory to medical therapy and related clinical signs and symptoms:
  • Hypercalcemia
  • Uncontrollable hyperphosphatemia
  • Evidence of osteitis fibrosa by bone biopsy, classic radiologic findings, or bone metabolic markers
  • Enlarged ± nodular parathyroid glands (>500 mg)
  • Calciphylaxis
  • Intractable pruritis
  • Progressive calcification of blood vessels
  • Severe skeletal deformity
  • Severe bone pain
  • Anemia resistance to erythropoietin
  • Peripheral neuropathy
• Sustained intact PTH levels >1,000 pg/mL refractory to medical therapies regardless of symptoms
	• Severe and persistent hypercalcemia ≥11.5 mg/dL for ≥6-12 mo and
	• Symptomatic/progressive hypercalcemia:
	  • Nephrolithiasis
	  • Persistent osteitis fibrosa
	  • Progressive vascular calcification
	  • Calciphylaxis
	  • Calcium-related renal graft function deterioration

KDIGO 2017 suggests parathyroidectomy "in patients with CKD G3a-G5D with severe hyperparathyroidism who fail to respond to medical or pharmacological therapy." Specific indications for parathyroidectomy listed are opinion based.

Abbreviation: PTH, parathyroid hormone.

- KDIGO 2017: Parathyroidectomy is suggested in patients with CKD G3a-G5D with severe hyperparathyroidism who fail to respond to pharmacologic therapy.
- Risks for post-PTX hungry bone syndrome and resultant hypocalcemia may include high kidney replacement therapy vintage, high preoperative serum phosphate and alkaline phosphatase, and postoperative decrease in PTH of 97% or more.
- For renal transplant candidates, decisions regarding parathyroidectomy and extent of resection should be jointly made with the transplant center, as sHPT (but likely not tertiary HPT) may resolve following a successful transplant.

DISORDERS OF MAGNESIUM METABOLISM

Background

- Mg^{2+} is the second most abundant intracellular and fourth most abundant cation in body.
- Approximately 99% of Mg^{2+} is stored in bones or within cells.
- In plasma, 70% to 80% of Mg^{2+} exists as free ionized Mg^{2+} and 20% to 30% as protein-bound or complexed.

Physiologic Functions of Magnesium

- Cofactor for enzymatic reactions requiring ATP (ATPase), "kinases"
- Enzyme activator for neuromuscular excitability and cell permeability
- Regulator of ion channels and mitochondrial function
- Critical element in cellular proliferation and apoptosis
- Important factor in both cellular and humoral immune reactions
- Cofactor for enzymes involved in modulation of transcellular glucose transport (magnesium deficiency may play a role in the development of glucose intolerance and diabetes mellitus type 2 and posttransplant diabetes mellitus)
- Protective effects of Mg^{2+} are thought to be via its anti-calcification property, thereby reducing both vascular calcification and kidney stone formation, antioxidant activity on endothelial function, and mesangial smooth muscle relaxation, among others.

Metabolism of Magnesium

Intestinal absorption

- Average daily intake approximately 300 mg/d
- Approximately 50% is absorbed from GI tract via:
  - Passive paracellular absorption driven by a high intraluminal concentration gradient
  - Active transport via transient receptor potential melastatin channel TRPM6 in large intestines where intraluminal Mg^{2+}

content is low. TRPM6 is also present in the DCT where it determines the final urinary Mg^{2+} content.

Cellular shift, redistribution

- Bones are the principal reservoirs of Mg^{2+} and do not readily exchange with extracellular Mg^{2+}. In negative Mg^{2+} balance, bone Mg^{2+} shifting into the plasma does not occur for weeks. Acute maintenance of plasma Mg^{2+} relies on renal reabsorption.
- Cellular influx increases with catecholamines, refeeding syndrome, treatment of metabolic acidosis, hungry bone syndrome seen after parathyroidectomy, or diffuse osteoblastic metastases.
- Redistribution: Mg^{2+} deposition in necrotic tissues, for example, acute pancreatitis

Output

- There is a physiologic intestinal Mg^{2+} loss of approximately 40 mg/d from pancreatic and salivary secretions. Magnesium loss is increased with chronic diarrhea and steatorrhea.
- Renal excretion

Renal Metabolism of Magnesium (Figure 3.9)

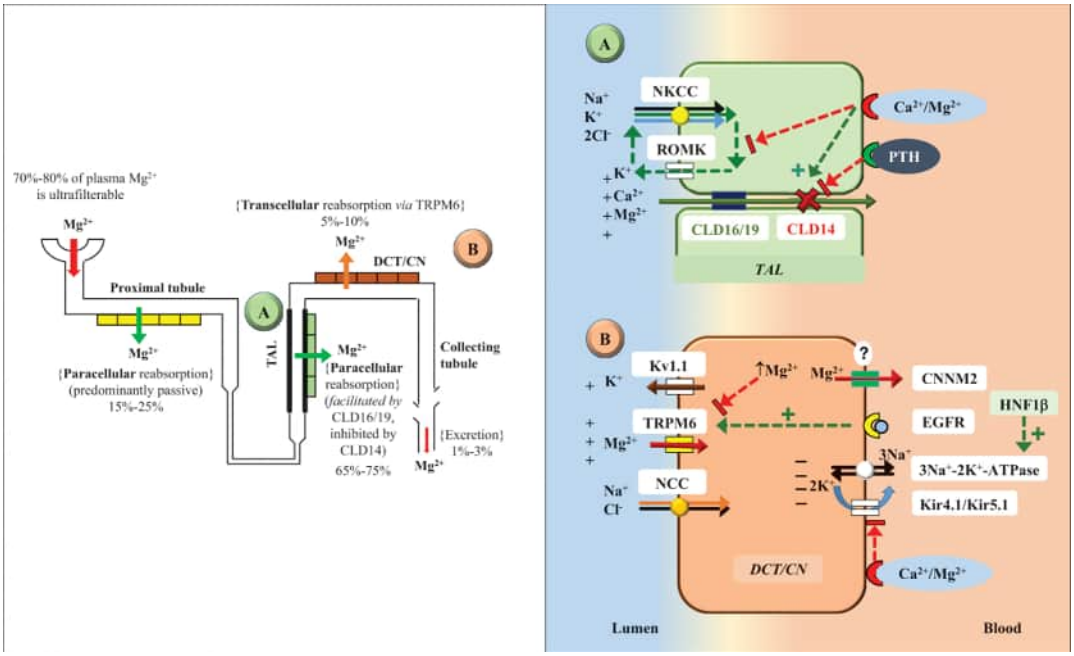


FIGURE 3.9 **Renal handling of magnesium.** A. Paracellular reabsorption of Mg^{2+} at TAL is similar to that for Ca^{2+}. B. In the DCT/CN, Kv1.1 and Kir4.1/Kir5.1 are thought to maintain the favorable transmembrane potential difference for Mg^{2+} reabsorption. Elevated serum Mg^{2+} level sensing by Ca^{2+}/Mg^{2+}-SR leads to inhibition of Kir4.1/Kir5.1; epithelial growth factor binding to its receptor EGFR stimulates the shuttling of cytosolic TRPM6 to the apical surface for Mg^{2+} reabsorption. The molecular mediator of basolateral Mg^{2+} reabsorption remains unknown.

Abbreviations: Ca^{2+}/Mg^{2+}-SR, calcium-/magnesium-sensing receptor; CLD, claudin; CNNM2, divalent metal cation transporter; DCT/CN, distal convoluted tubule/connecting segment; EGFR, epithelial growth factor receptor; HNF1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; NCC, sodium chloride cotransporter; NKCC, sodium-potassium 2 chloride cotransporter; PTH, parathyroid hormone; ROMK, renal outer medullary potassium channel; TAL, thick ascending limb of Henle loop; TRPM6, transient receptor potential melastatin channel 6.

Glomerular filtration

- About 70% to 80% of plasma Mg^{2+} is ultrafilterable in the ionic form
- Ultrafilterability of Mg^{2+} is dependent on glomerular filtration, volume and acid-base status, serum content of anions, and glomerular basement membrane integrity.

Proximal tubules

Around 15% to 25% of filtered Mg^{2+} is reabsorbed paracellularly, presumed to be mainly passive and proportional to Na^+ and H_2O reabsorption.

Thick ascending limb loop of Henle

- About 65% to 75% of filtered Mg^{2+} is reabsorbed paracellularly at TALH, a process driven by the positively charged lumen generated by K^+ recycling through ROMK and facilitated by the tight junction protein complex claudin-16/19.
- Claudin-14 reduces TALH cation permeability, thereby reducing Ca^{2+} and Mg^{2+} reabsorption.

Distal convoluted tubule/connecting segment

Approximately 5% to 10% of filtered Mg^{2+} (or 70%-80% of Mg^{2+} delivered from TALH) is reabsorbed via TRPM6 (see **Figure 3.9**).

Kv1.1 and Kir4.1/Kir5.1: The apical potassium voltage-gated channel Kv1.1 and basolateral potassium channel Kir4.1/Kir5.1 are thought to function to maintain the favorable transmembrane potential difference for Mg^{2+} reabsorption across TRPM6 in the DCT/CN segment.

Basolateral $3Na^+$-$2K^+$-ATPase: The basolateral $3Na^+$-$2K^+$-ATPase maintains the intracellular negative charge to promote intracellular Mg^{2+} uptake via TRPM6. The hepatic nuclear factor HNF1β regulates the transcription of Na^+-K^+-ATPase. Reduced HNF1β expression or activity can lead to hypomagnesemia.

Regulation of TRPM6 activity and expression

- High intracellular Mg^{2+} reduces TRPM6 apical expression.
- Epithelial growth factor (EGF) binding to its receptor EGFR increases activation and apical expression of TRPM6. This explains the reason for increased hypomagnesemia risk among patients receiving anti-EGFR monoclonal antibody therapy.
- Other suggested regulators: PTH, aldosterone, low dietary magnesium intake

Basolateral transport: The mechanism for basolateral Mg^{2+} extrusion remains to be defined.

HYPOMAGNESEMIA

Clinical Manifestations of Hypomagnesemia

Signs/symptoms (typically <1.2 mg/dL)

- Muscular tremors, fasciculations, nystagmus, tetany, altered mentation, depression, psychosis, migraine, ataxia, vertigo, seizures, dysphagia, asthma, chronic fatigue syndrome
- ECG changes
  - Prolonged QT and PR intervals
  - Flattening or inversion of precordial P waves
  - ST-depression, T-wave inversion
  - Widening of QRS, torsades de pointes
  - Treatment-resistant ventricular fibrillation and other arrhythmias
  - Worsening of digitalis toxicity

Other associated adverse effects

Altered glucose homeostasis, increased insulin resistance, atherosclerotic vascular disease, HTN, myocardial infarction, osteoporosis and fractures, worse GFR decline in patients with diabetes type 2 and CKD, worse recovery potential in AKI in intensive care unit (ICU) setting, asthma, osteoporosis

Electrolyte Disturbances Associated With Hypomagnesemia

Hypokalemia

- Mg^{2+} keeps ROMK closed. The lack of Mg^{2+} leads to K^{+} leakage via ROMK.
- Hypokalemia may intefere with the generation of the favorable potential gradient that facilitates Mg^{2+} reabsorption at DCT/CN, thereby contributing to hypomagnesemia.
- Concurrent hypokalemia and hypomagnesemia may be induced by the same condition, hyperaldosteronism.

Hypocalcemia

Hypomagnesemia is associated with impaired PTH secretion and tissue sensitivity to PTH, both leading to hypocalcemia.

Causes of Hypomagnesemia

Acquired and congenital causes of hypomagnesemia are summarized in **Tables 3.6 and 3.7**.

Table 3.6 Congenital causes of hypomagnesemia

	Level of defect	Specific defect	Conditions
Intestinal absorption	Passive paracellular and transcellular via TRPM6	TRPM6	Hypomagnesemia with secondary hypocalcemia
Cellular shift/tissue sequestration	—	—	—
Renal handling	Glomerular filtration	—	—
	Proximal tubular reabsorption	?	—
	Thick ascending limb of Henle loop	Claudin-16/19	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
		NKCC2	Antenatal Bartter syndrome type 1 with low to normal serum magnesium
		ROMK	Antenatal Bartter syndrome type 2 with low to normal serum magnesium
		ClC-Kb	Classic Bartter syndrome type 3, hypomagnesemia in ~20%
		Gain-of-function	Bartter syndrome type 5

	Level of defect	Specific defect	Conditions
		CaSR	
	Distal convoluted tubule and connecting segment	TRPM6	Hypomagnesemia with secondary hypocalcemia
	Apical regulators/effects of TRPM6	Kv1.1	Isolated autosomal dominant hypomagnesemia
		Kir4.1/Kir5.1	Kir4.1 mutation: SeSAME/EAST syndrome; Kir5.1 mutation: hypomagnesemia, hypokalemia, hyperchloremic metabolic acidosis and hypercalciuria
		NCC	Gitelman syndrome
	Basolateral regulators/effectors of TRPM6	Na^+-K^+-ATPase	FXYD2 (gene encoding Na^+-K^+-ATPase): autosomal dominant hypomagnesemia with hypocalciuria **HNF1**β: renal cysts and diabetes mellitus with renal magnesium wasting and hypocalciuria Isolated dominant hypomagnesemia: autosomal dominant mutation of γ-subunit of Na^+-K^+-ATPase leading to urine Mg^{2+} wasting but hypocalciuria.
		EGFR	Isolated recessive hypomagnesemia with normocalciuria
		CNNM2	Autosomal dominant hypomagnesemia
		Insulin	TRPM6 polymorphisms associated with reduced insulin activation of TRPM6,

	Level of defect	Specific defect	Conditions
			particularly if low dietary magnesium intake

Abbreviations: CaSR, calcium-sensing receptor; ClC-Kb, chloride channel; CNNM2, divalent metal cation transporter; EGFR, epithelial growth factor receptor; HNF-1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; NCC, sodium chloride cotransporter; NKCC2, sodium-potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; TRPM6, transient receptor potential melastatin channel 6.

Table 3.7 Acquired causes of hypomagnesemia

	Level of defect	Specific defect	Condition
Intestinal absorption	Passive paracellular and transcellular via TRPM6	TRPM6	Malnutrition; prolonged nasogastric suction; malabsorptive conditions; short gut syndrome; alcoholism; use of proton pump inhibitors
Cellular shift/tissue sequestration	—	—	Acute pancreatitis (Mg^{2+} and Ca^{2+} saponification in necrotic fat); hungry bone syndrome; refeeding; foscarnet; massive blood transfusions; third trimester pregnancy; lactation; parenteral alimentation; cardiopulmonary bypass
Renal handling	Glomerular filtration	—	Hyperfiltration (diabetes mellitus [DM], osmotic or post-obstructive or ATN diuresis); large volume expansion with fluid administration; increased filterable Mg^{2+} (eg, seen with metabolic acidosis)
	Proximal tubular reabsorption	—	Fanconi syndrome; drug toxicity (cisplatin, gentamicin, pentamidine); high dietary sodium intake

	Level of defect	Specific defect	Condition
	Thick ascending limb of Henle loop	Claudin-16/19	—
		NKCC2	Loop diuretics; hypokalemia
		ROMK	Hypokalemia
		ClC-Kb	—
		CaSR	Increased serum Mg^{2+} and Ca^{2+} levels; aminoglycosides; possibly calcimimetics
	Distal convoluted tubule Connecting segment	TRPM6	Calcineurin inhibitors: cyclosporine and tacrolimus reduce renal TRPM6 expression; rapamycin reduces TRPM6 stability
	Apical regulators/effects of TRPM6	Kv1.1	Hypokalemia
		Kir4.1/Kir5.1	Hypokalemia
		NCC	Thiazide diuretics; calcineurin inhibitors
	Basolateral regulators/effectors of TRPM6	Na^+-K^+-ATPase	Hypophosphatemia; cyclosporine has been shown to inhibit Na^+-K^+-ATPase; ethanol inhibits Na^+-K^+-ATPase.
		EGFR	Anti-EGF receptor antibodies (cetuximab, panitumumab, matuzumab); cisplatin reduces EGF and TRPM6 mRNA; cyclosporin reduces TRPM6, NCC, and EGF mRNA
		CNNM2	—
		Insulin	DM

Abbreviations: ATN, acute tubular necrosis; CaSR, calcium-sensing receptor; ClC-Kb, chloride channel; CNNM2, divalent metal cation transporter; EGFR, epithelial growth factor receptor; HNF-1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; NCC, sodium chloride cotransporter; NKCC2, sodium-potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; TRPM6, transient receptor potential melastatin channel 6.

Decreased intake or intestinal absorption or both

- Malnutrition, prolonged intravenous therapy without Mg^{2+} supplementation
- Surgical resection of small intestine, familial Mg^{2+} malabsorption (TRPM6)

Cellular shift/redistribution

- Acute pancreatitis (Mg^{2+} and Ca^{2+} saponification in necrotic fat)
- Hungry bone syndrome; refeeding
- Foscarnet (likely because foscarnet is a strong chelator of divalent cations)
- Massive blood transfusions
- Third trimester of pregnancy; lactation
- Parenteral alimentation
- Cardiopulmonary bypass

Excessive GI fluid loss

Prolonged nasogastric suction, ulcerative colitis, laxative abuse, intestinal and biliary fistulas

Excessive urinary losses

Glomerular hyperfiltration/high urine flow: glomerular hyperfiltration, volume expansion, diuretics, post-obstructive, posttransplant diuresis, increased filterable Mg^{2+} load (eg, seen with metabolic acidosis)

Electrolyte disturbances: hypercalcemia, renal tubular acidosis, hypophosphatemia

Drugs

- Aminoglycosides, amphotericin, cisplatin ≫ carboplatin, cyclosporine, epidermal growth factor inhibitors (eg, cetuximab, panitumumab, matuzumab), antituberculosis drugs (eg, capreomycin), ritodrine, β-adrenergic agonists (eg, theophylline, salbutamol), other drugs (amphotericin B, pentamidine, foscarnet, pamidronate)
- The use of proton pump inhibitors has been reported to be associated with hypomagnesemia. This is exacerbated with concurrent diuretic use. Single-nucleotide polymorphisms in TRPM6 have been attributed to the increased hypomagnesemia risk.

Congenital disorders

TRPM6: autosomal recessive mutation of TRPM6 leading to hypomagnesemia with secondary hypocalcemia

- Hypomagnesemia is due to reduced intestinal transcellular Mg^{2+} absorption and renal Mg^{2+} reabsorption at DCT via TRPM6. Hypomagnesemia reduces PTH secretion and skeletal responsiveness to PTH.
- Affected individuals may present with seizures/tetany perinatally.
- Treatment: high-dose oral magnesium sulfate for absorption via paracellular pathway

Claudin-16/19: autosomal recessive mutation of claudin-16 or claudin-19 leading to familial hypomagnesemia with hypercalciuria and nephrocalcinosis due to renal Mg^{2+} and Ca^{2+} wasting

EGF: Normal EGF binding to its receptor EGFR is necessary for normal trafficking of TRPM6 to the apical surface in DCT. Mutation of EGF or pro-EGF or presence of antibodies directed against EGFR (eg, cetuximab, panitumumab, matuzumab) can cause urinary Mg^{2+} wasting.

NCC: Dysfunction/mutation of NCC (Gitelman syndrome) may reduce TRPM6 expression and causes severe renal Mg^{2+} wasting.

FYI

Other congenital disorders associated with hypomagnesemia

- γ-Subunit of Na^+-K^+-ATPase (isolated dominant hypomagnesemia [IDH]): autosomal dominant mutation of γ-subunit of Na^+-K^+-ATPase leading to urine Mg^{2+} wasting but hypocalciuria. Affected individuals have hypomagnesemia but normal serum Ca^{2+} and K^+.
- Hepatic nuclear factor 1-β mutation (HNF1β) regulates transcription of the gene encoding γ-subunit of Na^+-K^+-ATPase. Patients present similarly as IDH.
- Potassium voltage-gated channel Kv1.1 mutation reduces K^+ exit into lumen, hence reduced positive voltage that would normally favor Mg^{2+} entry via TRPM6.
- Inward rectifying potassium channel Kir4.1/5.1: Loss of function reduces basolateral K^+ recycling, hence reduced $3Na^+$-$2K^+$-ATPase activity that normally generates the negative intracellular voltage for apical Mg^{2+} entry.

Other causes of hypomagnesemia

Acute pancreatitis, transfusion of citrated blood, severe burns, continuous ambulatory peritoneal dialysis, chronic alcoholism

Diagnosis of Hypomagnesemia

Total magnesium urinary loss in hypomagnesemia

- Urinary magnesium more than 20 mg/d indicates urinary Mg^{2+} wasting.
- Urinary magnesium less than 10 mg/d indicates total body Mg^{2+} depletion.

Urinary Mg excretion may be measured as fractional excretion of Mg (FeMg)

- FeMg = [(Urine Mg × SCr) ÷ (0.7 × serum Mg × urine Cr)] × 100.
- Factor of 0.7 indicates only approximately 70% of plasma Mg is filterable.
- Equation should only be used in patients with relatively good kidney function.
- FeMg more than 2% to 4% indicates excessive renal Mg^{2+} wasting (eg, renal causes).
- FeMg less than 2% to 2.5% indicates extrarenal causes of hypomagnesemia (eg, intestinal causes).

- See **Table 3.8**, for a summary of indices used in the diagnosis of magnesium disorders.

NOTE

The site of renal magnesium loss may be determined based on urinary calcium.

- Conditions involving defective magnesium reabsorption at the loop of Henle will have concurrent **hyper**calciuria, that is, urinary calcium more than 250 mg/d. Examples include loop diuretics, CaSR agonists (eg, gentamicin, cinacalcet), familial hypomagnesemia with hypercalciuria, and nephrocalcinosis (claudin-16/19 mutations).
- Conditions involving defective magnesium reabsorption at DCT present with **hypo**calciuria, that is, urinary calcium less than 200 mg/d. Examples include thiazide diuretics, Gitelman syndrome, and isolated dominant hypomagnesemia.

Table 3.8 Indices used in the diagnosis of magnesium disorders

Diagnostic testing	Description	Interpretation

24-h Urine Mg^{2+} collection	• 24-h urine collection
	• Also check urine creatinine to assess collection adequacy.
		• >20 mg/d is considered high urinary Mg^{2+} excretion.
		• <10 mg/d indicates total body Mg^{2+} depletion.
		• Examples for clinical application:
		  • For hypomagnesemia, >20 mg/d may be consistent with renal wasting.
		  • For hypermagnesemia, >20 g/d may be consistent with excess intake, exogenous source of magnesium.

Diagnostic testing	Description	Interpretation

Percent fractional excretion of Mg^{2+} (FeMg)	• FeMg = (UMg × SCr) ÷ (0.7 × SMg × UCr) × 100
	  • The 0.7 factor indicates that only ~70% of plasma Mg^{2+} is filterable.
	  • Equation should only be used for patients with relatively good kidney function.
		• FeMg >2%-4% is considered high urinary Mg^{2+} excretion.
		• FeMg ≤2%-2.5% is considered low urinary Mg^{2+} excretion.
		• Examples for clinical application:
		  • For hypomagnesemia, <2% may be consistent gastrointestinal loss with/without malnutrition.
		  • For hypermagnesemia, >2% may be consistent with excess intake, exogenous source of magnesium.

Abbreviations: SCr, serum creatinine; SMg, serum magnesium concentration; UCr, urine creatinine; UMg, urine magnesium concentration.

Management of Hypomagnesemia

Intravenous magnesium supplementation

- Severe symptomatic hypomagnesemia (eg, hemodynamic instability, arrhythmias, torsades de pointe)
- Severe hypomagnesemia with serum magnesium level less than 1 mg/dL (0.8 mEq/L or 0.4 mmol/L)
- Inability to tolerate oral magnesium

Oral magnesium supplementation

- Mild-to-moderate asymptomatic hypomagnesemia in patients who can tolerate oral magnesium
- Sustained-release magnesium formulations (eg, magnesium chloride or l-lactate) are preferred over magnesium oxide for slow absorption thereby minimizing renal loss. Diarrhea is a common side effect with magnesium oxide.

Epithelial sodium channel (ENaC) inhibitors

Amiloride inhibits Na^+ reabsorption at the DCT, collecting tubules, and collecting ducts, thereby enhancing the intraluminal positive charge that facilitates Mg^{2+} reabsorption.

SGLT2 inhibitors

The use of SGLT2 inhibitor has been shown to be associated with higher serum Mg^{2+} levels. This effect may be related to reduced insulin and increased glucagon levels, leading to increased extracellular Mg^{2+} shift and increased renal Mg^{2+} reabsorption, respectively.

Mineralocorticoid receptor antagonists

Aldosterone has been suggested to induce renal Mg^{2+} wasting, an effect that may be ameliorated by mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone).

NOTE

- Intravenous magnesium supplementation causes an abrupt rise in serum Mg^{2+} level, which leads to reduced reabsorption of Mg^{2+} across the TALH. This limits efficient magnesium repletion with intravenous supplementation.
- CAUTION with excessive Mg^{2+} supplementation:
  - Drug interactions: central nervous system (CNS) depressants (barbiturates, hypnotics, narcotics, antihistamines, antidepressants); cardiac glycosides; neuromuscular-blocking agents (pancuronium)
  - Side effects related to overdosing: flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and CNS depression proceeding to respiratory paralysis. Hypocalcemia with signs of tetany secondary to $MgSO_4$ therapy for eclampsia has been reported.
  - Amiloride may be considered in patients with thiazide or Gitelman-associated hypomagnesemia.

HYPERMAGNESEMIA

Clinical Manifestations of Hypermagnesemia

Signs/symptoms: muscular weakness, paralysis, ataxia, drowsiness, confusion, paralytic ileus, bladder paralysis, nausea/vomiting,

hypotension, bradycardia, absent tendon reflexes, and hypoventilation —essentially, everything "slows down"

Associated electrolyte changes: hypocalcemia (due to suppressed PTH secretion and possible Mg^{2+} binding and activation of CaSR)

ECG changes

- Increased PR and QT
- Increased QRS duration
- Variable decrease in P-wave voltage
- Variable degree of T-wave peaking
- Complete atrioventricular block, asystole

Other effects

- Hypoparathyroidism, vascular relaxation, interference with platelet adhesiveness, thrombin generation time, and clotting time
- Hyperkalemia may be associated with hypermagnesemia. This is possibly due to Mg^{2+}-gate keeping function in ROMK: Mg^{2+} normally keeps ROMK closed and limits K^+ wasting.

Causes of Hypermagnesemia

Excessive intake: oral, infusion, magnesium containing enemas, Dead Sea water drowning (very high content of both calcium and magnesium), urethral irrigation; use of common Mg^{2+}-containing medications, especially among patients with CKD: laxatives (milk of magnesia), antacids (eg, extra-strength Rolaids, Mylanta), or even in some multivitamins

Redistribution/extracellular shift: acute acidosis, rhabdomyolysis, tumor lysis

Excretion failure: kidney failure

Others: FHH, diabetic ketoacidosis, lithium toxicity, adrenal insufficiency, hypothyroidism

Management of Severe Symptomatic Hypermagnesemia

Antagonizing magnesium

- Calcium is a natural antagonist of Mg^{2+}.
- Calcium: approximately 100 to 200 mg elemental Ca^{2+} infused over 5 to 10 minutes
- One 10-mL ampule of Ca^{2+} gluconate contains 90 mg of elemental calcium.
- One 10-mL ampule of Ca^{2+} chloride contains 272 mg of elemental calcium.

Magnesium removal

- Dialysis
- Diuresis with furosemide (**NOTE**: Loop diuretics can lower Ca^{2+}, which may precipitate arrhythmias in patients with hypermagnesemia.)

Cardiopulmonary support

NOTE

- Magnesium can potentiate the hypotensive effect of CCB and can cause severe hypotension in patients with preeclampsia/eclampsia treated with both. Treatment of this complication is administration of calcium gluconate.
- Both hypo- and hypermagnesemia can reduce PTH secretion.

KIDNEY STONES

Definitions

- Nephrolithiasis refers to *intratubular* stone deposits.
- Nephrocalcinosis refers to calcium deposits in renal parenchyma and tubules in cortex and medulla.

- Both may occur in the same patient.

Epidemiology

National Health and Nutrition Evaluation Survey (NHANES) involving 10,521 participants age 20 to 59, 2017 and 2018 data:

- The prevalence of kidney stones increased steadily from 6.5% in 2007 and 2008 data cycle to 9.4% in the 2017 and 2018 cycle.
- The 12-month incidence of kidney stones was 2.1% or 2,054 stones per 100,000 adults.
- Men have a higher prevalence than women, 13.0% versus 9.5%, respectively, in the 2015 to 2016 NHANES data cycle, but the gender gap appears to be narrowing.
- Race: Non-Hispanic Blacks and Hispanics had the lowest prevalence in latest NHANES data set.
- Factors associated with stone recurrence that are commonly reported include younger age, higher body mass index, family history of stones, and uric acid stone.

Risks

Geography: Southeastern states of the United States have the highest risk (hot temperature, sunlight, humidity).

Occupation: exposure to hot weather, dehydration, chemicals (eg, cadmium, trimethyltin chloride, oxalic acid, ethylene glycol)

Physical characteristics: increasing age, high body mass index, high total and truncal body fat as measured by DEXA

Systemic conditions

Obesity and diabetes mellitus

- Lack of insulin is associated with low urine pH (increased risk of uric acid stones).

- Fatty liver has been suggested to downregulate alanine-glyoxylate aminotransferase (AGXT), an enzyme that normally reduces the generation of oxalate. Lowering of AGXT, therefore, increases blood oxalate level and oxaluria (increased risk of calcium oxalate stones).

CVD, eg, CHD and stroke

- Alteration in calcium metabolism may precipitate calcifications in both conditions.
- Increased oxidative stress leading to calcifications in endothelial cells and tubular epithelial cells leads to CVD and stone formation, respectively.

Hypertension

Having kidney stones is associated with increased HTN and CKD risks (not vice versa), likely due to associated kidney injury (eg, obstruction, use of non-steroidal anti-inflammatory drugs [NSAIDs], nonhealthy lifestyle leading to stone formation).

Gout is not necessarily associated with increased risk for uric acid stone formation.

- Gout or hyperuricemia due to hypouricosuria does not increase risk for uric acid stones.
- Gout or hyperuricemia associated with metabolic syndrome or increased uric acid production may have increased risk of uric acid stones. Regardless, low urine pH is the most important factor for uric acid precipitation.

Stone Types and Prevalence in the United States

Calcium (70%-90%): Mixed calcium oxalate and phosphate is most common stone, followed by calcium oxalate and calcium phosphate.

Uric acid (5%-10%): The incidence of uric acid stone is on the rise in the United States and thought to be associated with the increased incidence of metabolic syndrome.

Struvite (<10%)

Cystine and other (<1%)

Common crystals associated with kidney stones are shown in **Figure 3.10.**

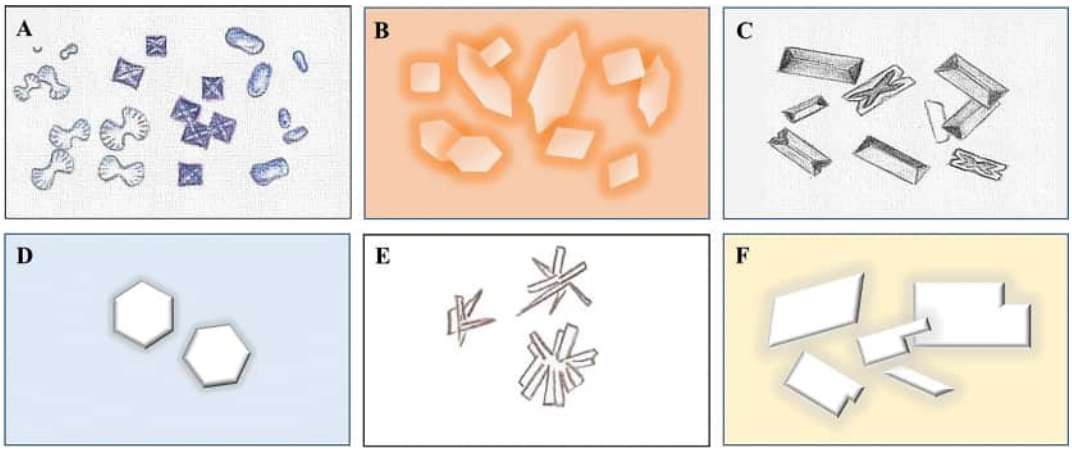


FIGURE 3.10 Stone crystals. A. Calcium oxalate crystals (octahedral, dumbbell, or picket fence-shaped) may be seen with ethylene glycol toxicity or hypercalcemia. B. Uric acid crystals (platelike, rhomboid, or square-shaped) may be seen in urine pH less than 7.0 and tumor lysis syndrome. C. Struvite crystals ("coffin lid" or fern-leaflike if freshly formed) consist of ammonium, magnesium, and phosphate. D. Cystine crystals (hexagonal) may be seen in cystinosis but not in normal urine. E. Calcium phosphate crystals (blunt-ended needles, prisms, or rosette) may also appear amorphous similar to urate crystals but calcium phosphates precipitate at basic urine pH more than 7.0 rather than low pH. Additionally, unlike the pinkish color with urate, calcium phosphate crystals are colorless or white. F. Cholesterol plates.

Stone Promoters

Randall plaque: Subepithelial calcification in the renal papilla that act as an anchor for calcium oxalate crystals and is considered to be the initiating event in renal stone formation.

Urinary factors

Sodium: High dietary sodium intake has been shown to downregulate NHE3 and Na^+-dependent P_i cotransporters (Na-Pi 2a and Na-Pi 2c), thereby increasing calciuria and hyperphosphaturia, respectively, and risk of calcium stone formation.

Urine pH

- Low urine pH facilitates uric acid and cystine stone precipitation.

- High urine pH facilitates calcium phosphate precipitation. NOTE: Although triple phosphate stones (aka, magnesium ammonium phosphate or struvite) are seen in high urine pH, it is the ammonia concentration that is the primary factor for the triple phosphate crystals formation. Alkalinization of a urine specimen with ammonia generates triple phosphates, while alkalinization with sodium hydroxide does not.

Stone substrates: High levels of stone substrates: calcium, oxalate, urate, phosphate, cystine

Low urine flow

Bacterial products

Others

- Metabolic syndrome (uric acid > calcium oxalate)
- Bariatric surgeries, 2016 meta-analysis: Roux-en-Y is associated with increased risk for kidney stones. Patients have increased oxalate and calcium oxalate excretion at 6- and 12-month follow-up, presumably due to increased intestinal fat malabsorption. Calcium preferentially binds to free fatty acids in the gut, thereby allowing free oxalate to be absorbed. Restrictive band surgery was associated with decreased stone risk.
- Dietary factors associated with higher stone risks:
  - Supplemental (not dietary) vitamin C intake more than 1,000 mg/d is associated with increased incident kidney stones in men but not in women (Nurses' Health Study I and II and Health Professionals Follow-Up Study). Vitamin C is converted to oxalate and renally excreted.
  - Supplemental (NOT dietary) calcium
  - Others: dietary oxalate, sucrose, fructose, sugar-sweetened soda, punch

Stone Inhibitors

Inorganic factors

Mg^{2+}

- Mg^{2+} complexes with oxalate, thereby decreasing calcium oxalate supersaturation.
- Mg^{2+} may also reduce gut oxalate absorption.
- Higher dietary Mg^{2+} has been shown to be associated with a 30% lower risk of stone formation in men, but not in women.

Pyrophosphate: Pyrophosphate forms highly soluble complexes with Ca^{2+}.

Citrate: Citrate binds to Ca^{2+} to form a soluble complex in the urine, thus effectively reduces Ca^{2+} availability for calcium phosphate/oxalate formation.

Organic factors: nephrocalcin, urinary prothrombin fragment 1, protease inhibitor: inter-α-inhibitor, glycosaminoglycans

High urine flow: MOST effective inhibitor (ie, intervention) in stone prevention

Dietary factors: associated with lower stone risks: dietary calcium 1,000 to 1,200 mg/d (dairy and nondairy), dietary potassium, DASH (Dietary Approaches to Stop Hypertension) diet, Mediterranean diet (rich in fruits, vegetables [source of citrate, potassium, and fiber], nuts, fish, and legumes), limited animal protein (0.8-1.0 g/kg/d), low saturated fats and sugars, moderate alcohol, coffee (regardless of caffeine content), tea, orange juice (source of citrate), zinc (eg, oysters, beans, mushrooms, cashews), phytates (stored form of phosphorus found in seeds, nuts, legumes, whole grains)

Table 3.9 summarizes kidney stone promoters and corresponding management options for different stone types.

Table 3.9 Stone risks and management options

Stone type	Risks	Management options
All stones	Low urine volume	• Fluid intake to produce >2.5 L of urine volume daily • Protective fluids: coffee, tea, beer, wine, orange juice

Stone type	Risks	Management options
		• Fluids with potential increased stone risks: sugar-sweetened sodas, fruit punch, grapefruit juice (increase in urinary citrate but also oxalate), cranberry juice (minimal increase in citrate but also increase in urinary calcium and oxalate)
Calcium oxalate and calcium phosphate	Hypercalciuria	• Evaluate and treat primary hyperparathyroidism or granulomatous disease. • Maintain *normal dietary* calcium intake (eg, 1,000 mg/d)—dietary calcium restriction is NOT recommended. • Limited animal protein (0.8-1.0 g/kg/d) • Thiazide diuretics with/without low-dose K^+-sparing amiloride • [a]K-citrate or K-HCO_3 (10-20 mmol bid to tid) as safely tolerated. Do not use Na^+-alkali salts as Na^+ load can increase urinary Ca^{2+} excretion. • [b]Neutral orthophosphate (eg, K-phos neutral, 1.0-2.5 g/d in divided doses tid to qid)
	High urine sodium	• Dietary sodium restriction to <100 mmol/d (<2.3 g/d)
	Hypocitraturia	• Encourage high citrate diet, citric fruit juices (orange juice > lemonade). • Consider K-citrate (10-20 mmol bid to tid) as safely tolerated. Do not use Na^+-alkali salts as Na^+ load can increase urinary Ca^{2+} excretion.
	Hyperuricemia	• Allopurinol if recurrent calcium oxalate stones in the absence of hypercalciuria or hyperoxaluria

Stone type	Risks	Management options
		• [c]Restriction of nondairy protein (high uric acid–containing proteins)
	Other	• Replace magnesium and/or potassium if low serum magnesium and/or potassium levels.
Calcium oxalate	Hyperoxaluria	• [d]Dietary oxalate restriction • Continue dietary oxalate restriction only if it effectively reduces urinary oxalate level. • Avoid ingestion of >500 mg/d of ascorbic acid.
	Primary hyperoxaluria	• Lumasiran for primary hyperoxaluria type 1 • Pyridoxine (250-500 mg/d), orthophosphate (40-60 mg/kg/d), K-citrate (0.15 g/kg) with/without magnesium oxide (500 mg/d/m^2) • Combined liver and kidney transplant as clinically indicated
	Inflammatory bowel	[e]Cholestyramine
Calcium phosphate	Hyperphosphaturia	Beneficial effect of dietary phosphate restriction has not been shown.
	High urine pH (eg, >7.0)	• No treatment for high urine pH • Reduce K-citrate dose if this agent is being used.
Uric acid	Hyperuricemia	• Allopurinol or febuxostat • [c]Avoid high uric acid–containing proteins.
	Low urine pH	• [a]K-citrate 10-20 mmol bid to tid; uptitrate as needed and safely tolerated; Consider tid frequency to minimize intermittent pH-lowering

Stone type	Risks	Management options
		episodes when uric acid may precipitate.
Triple phosphate (aka, magnesium ammonium phosphate, struvite)	Genitourinary tract abnormality with recurrent urinary tract infections	• Correction of anatomical tract abnormality if possible • Treatment of underlying infection • Stone removal • [f]Urease inhibitor acetohydroxamic acid (Lithostat) 250 mg tid to qid
Cystine	High urine cystine level	• [g]High fluid intake, 3.5-5.0 L/d • Dietary restriction • [h]Use of drugs that can form soluble heterodimers with cysteine as last resort (D-penicillamine, tiopronin)
	Low urine pH	• K-citrate, 40-80 mmol/d in divided doses tid to qid to achieve urine pH >7.0.
2,8-Dihydroxyadenine	Adenine phospho-ribosyl-transferase deficiency	• Xanthine oxidase inhibitors: Start low dose of either allopurinol or febuxostat and uptitrate as needed to achieve disappearance of 2,8-dihydroxyadenine crystals in the urine.

[a]Avoid urine pH above 7.0, because alkaline urine favors calcium phosphate precipitation.

[b]Orthophosphates can increase serum phosphate and reduce 1,25$(OH)_2$D level.

[c]Proteins with high uric acid content: anchovies, sardines, herring, mackerel, scallops and mussels, waterfowl, organ meats, glandular tissue, and meat juice drippings or extracts.

[d]High oxalate diet: dark green leafy vegetables such as spinach and rhubarb, Swiss chards, nuts, chocolate.

[e]Cholestyramine binds both bile acids and oxalate, but its gastrointestinal side effects may limit routine use.

[f]Acetohydroxamic acid is associated with significant side effects. Its use should be limited to patients who cannot or refuse to undergo stone removal.

[g]Patients with cystine stone require much higher urine volume compared to those with all other stone types to inhibit stone formation.

[h]Side effects may limit medical therapy in patients with cystine stone.

The Role of Urinary Tract Bacteria and Microbiome in Kidney Stone Formation

Urea splitting organisms (urease producing organisms)

Proteus, Hemophilus, Yersinia, Klebsiella, Serratia, Citrobacter, Staphylococcus epidermidis, Ureaplasma urealyticum, Pseudomonas

Bacteria that may act as a nidus to promote calcium oxalate stone formation

Escherichia coli, *Staphylococcus aureus*, *Streptococcus pneumoniae*

Protective bacteria

Lactobacillus and Prevotella

Urinary tract microbiome

A diverse array of microorganisms in the urinary tract not detected by routine urine cultures, referred to as microbiomes, have also been implicated in affecting stone formation.

Clinical Manifestations

Pain depends on stone location.

- Intrarenal stone: asymptomatic unless pyelonephritis or obstruction with distention of renal capsule
- Proximal ureter: colicky flank or anterior abdominal pain
- Distal third ureter: flank pain radiating to groin/genitals
- Ureterovesicular junction: suprapubic pain, urgency, dysuria
- Bladder neck: suprapubic pain, anuria, gross hematuria

Hematuria: ranges from none to microscopic to gross hematuria

Pyuria: may be sterile due to inflammation (from stone or ureteral stent in place) or associated with concurrent urinary tract infection/pyelonephritis

General Dietary Advice

Fluid

Increase fluid intake to ensure urine output more than 2.5 L/d or a volume of approximately 3% of body weight (kg) daily. For example, a 70 kg person should drink enough fluid to ensure a urine volume of at least 0.03 × 70 = 2.1 L/d. This is not the same as telling patients to drink 2.1 L/d.

Avoid sucrose or fructose containing sodas, grapefruit juice (particularly if calcium oxalate stone, mechanism unknown), and large volume (eg, >1 L) of cranberry juice (minimal increase in urine citrate but with concurrent increase in calcium and oxalate). Coffee, tea, milk, and alcohol increase urine flow and reduce stone risk. Orange juice can increase urinary citrate level, which is protective against calcium stones.

Diet

Calcium and potassium: Normal calcium, high fruits and vegetables with high potassium content, and low animal protein diet or DASH diet are associated with lower stone risk. Increased fruits and vegetables intake increases citrate excretion, thereby increasing urine pH and luminal citrate concentration. This is beneficial to patients with uric acid and calcium stone.

Sodium: Limit sodium intake below 100 mmol/d (2.4 g) sodium daily.

Animal protein: Avoid high animal protein intake due to:

- High acid load that reduces citrate excretion
- High acid load that promotes calcium leak from bones
- Increased urinary oxalate and uric acid excretion

Oxalate: Dietary oxalate restriction may be considered for calcium oxalate stones AND should only be *continued if* urine excretion of oxalate is effectively reduced (eg, avoid dark green leafy vegetables such as spinach, rhubarb, nuts, chocolate). If not effective, discontinue dietary oxalate restriction.

Vitamin supplements

Avoid high supplemental calcium, vitamin D, and vitamin C (metabolize to oxalate).

NOTE

Dietary calcium intake from either nondairy or dairy sources is protective against stones but not calcium supplement given in between meals. The former can bind and eliminate intestinal phosphate or oxalate from the diet, thereby reducing phosphate/oxalate absorption. The latter predominantly increases intestinal calcium absorption without the benefit of reducing any phosphate/oxalate absorption that occurs during meals. Dietary calcium restriction is NOT recommended. For patients who require calcium supplement for osteoporosis, monitor urine calcium and titrate calcium supplement to keep urine calcium excretion less than 70% of upper limit of normal (opinion based).

Special Notes for Specific Stone Types

Calcium stone

- Mixed calcium oxalate and phosphate are most common, followed by calcium oxalate, then calcium phosphate.
- High urine pH more than 6.5 facilitates calcium phosphate precipitation. Calcium oxalate precipitation is not affected by urine pH.
- Types of calcium phosphate stones:
  - Calcium apatite (main constituents of bones/teeth)
  - Calcium brushite (calcium monohydrate phosphate): physically resistant to extracorporeal shock-wave lithotripsy (ESWL); repeated treatments may be necessary
- Nephrocalcinosis associated with distal renal tubular acidosis (RTA) (type 1) is predominantly composed of calcium phosphates (**Figure 3.11**).

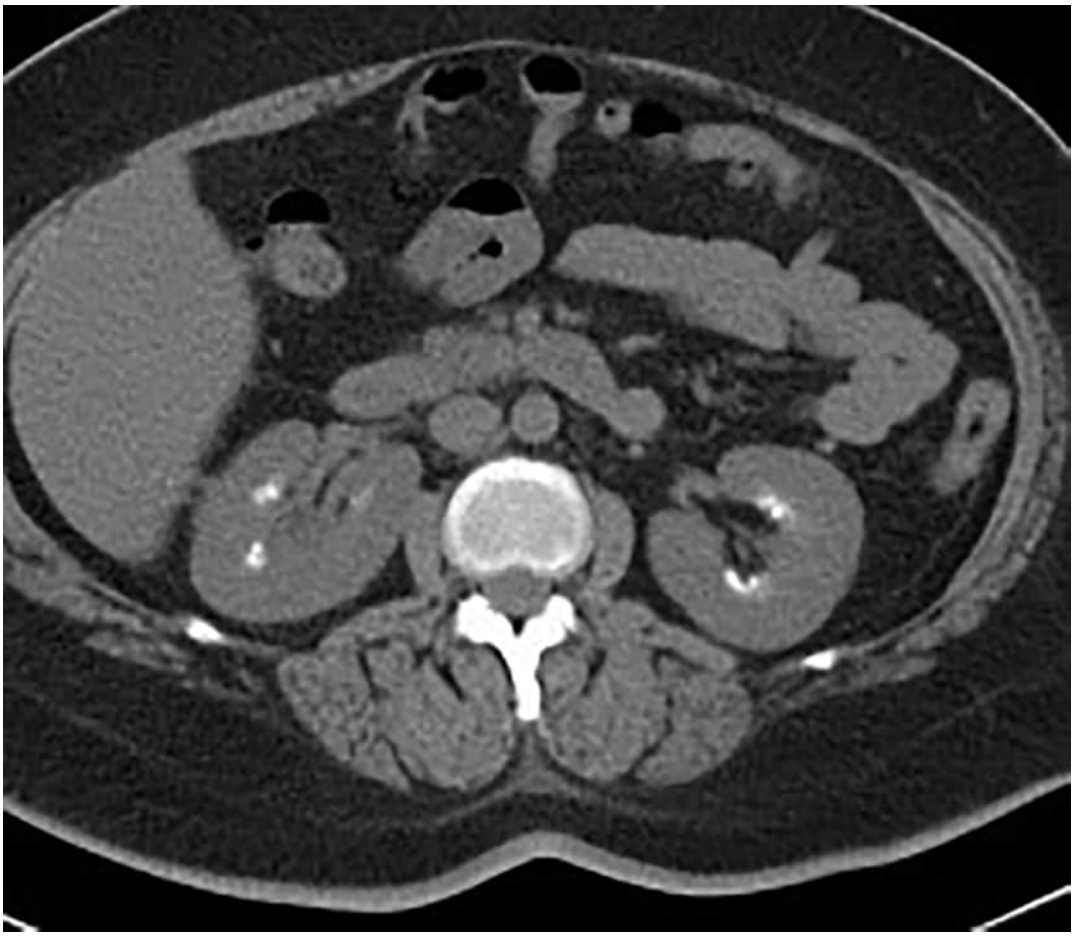


FIGURE 3.11 **Medullary nephrocalcinosis.** Axial and coronal noncontract computed tomogram showing amorphous and course pyramidal calcifications in both kidneys consistent with medullary nephrocalcinosis.

Metabolic risk factors for calcium stones

Hypercalciuria (most common risk for calcium stones)

FYI

Dent disease

- An X-linked recessive disorder that is characterized by low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, kidney stones, kidney failure, and rickets
- Hypercalciuria is thought to be due to increased intestinal calcium absorption and dysregulation of vitamin D metabolism.
- The majority of patients have mutation of CLCN5, the gene encoding the chloride-proton antiporter CLC-5, a protein involved in proximal tubular endocytosis and endosomal acidification. Some patients have mutation of OCRL1 gene encoding OCRL phosphatase, which plays a role in endosomal trafficking.
- Dent disease may be suspected in individuals with the following three characteristics:

- Low-molecular-weight proteinuria (tubular proteinuria)
- Hypercalciuria
- At least one of the following: nephrocalcinosis or nephrolithiasis, hematuria, hypophosphatemia, or CKD

- Dent disease may also be associated with focal global glomerulosclerosis (not the same as focal segmental glomerulosclerosis [FSGS], which is rare in patients with Dent disease).
- Despite increased intestinal calcium absorption, dietary calcium restriction is not recommended. Thiazide diuretics, dietary citrate, and oral phosphates may be considered.

- Hyperuricosuria: Dissolved uric acid salts appear to increase calcium oxalate precipitation via unclear mechanism(s).
- Phosphaturia: "renal phosphate leak" (eg, mutations of renal Na-Pi cotransporters, increased FGF23 activity)
- Hyperoxaluria
  - Dietary causes of hyperoxaluria:
    - Low dietary calcium allows free oxalate to be absorbed readily in the intestines followed by urinary excretion. In contrast, high dietary calcium intake, for example, dairy products, allows calcium to precipitate with oxalate from food sources, thereby minimizing intestinal oxalate absorption for stone formation.
    - High intake of protein, oxalate, or its precursors (ethylene glycol, methoxyflurane anesthesia, or large doses of ascorbic acid in susceptible individuals)
  - Enteric causes of hyperoxaluria:
    - Fat malabsorption (eg, inflammatory bowel disease/resection/bypass, exocrine pancreatic insufficiency). Undigested fatty acids bind calcium within the GI tract, hence less calcium availability to bind oxalate in the gut for elimination. This leads to increased intestinal oxalate absorption and urinary oxalate excretion.
    - Malabsorptive bariatric surgeries
  - Primary hyperoxaluria (PH):
    - Autosomal recessive disorders (types 1, 2, and 3 or primary hyperoxaluria type 1 [PH1], PH2, and PH3, respectively) due to

mutations of enzymes involved in hepatic glyoxylate metabolism, resulting in excessive production and urinary excretion of oxalate. Deposition of oxalate in bones, joints, bone marrow defines "oxalosis."

- There is wide outcome variability for patients with PH. Nonetheless, without aggressive therapy, death from kidney failure and oxalosis may occur. PH1 typically presents with ESKD in early adulthood if undiagnosed and untreated.
- Diagnosis is based on significantly elevated urine oxalate levels (ie, >2-3 times upper normal limit) and genetic analysis. The presence of urinary glycolate is suggestive of PH1, while elevated urinary levels of L-glyceric acid may be suggestive of PH2.
- Lumasiran is indicated for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients. See **Appendix A3.1**, for mechanism of action and reason why it is not effective in PH2 or PH3.
- Supportive therapy: high fluid intake and administration of calcium oxalate inhibitors, including neutral phosphate (orthophosphate 40-60 mg/kg/d), potassium citrate (0.15 g/kg), and/or magnesium oxide (500 mg/d/m^2). Combined (or sequential) kidney liver transplantation is suggested in PH1, while kidney alone transplant in PH2 is preferred.

- Other causes of hyperoxaluria:
  - Slc26a6 variant has been suggested to be associated with increased stone risk. Slc26a6 is a gene encoding a multifunctional anion transporter responsible for oxalate transport in both intestines and kidneys.
  - Presence of gut *Oxalobacter formigenes is thought to be protective against kidney stones: O. formigenes* are gram-negative bacteria that degrade gut oxalate.
- Hypocitraturia:
  - Citrate forms *soluble* complexes with Ca^{2+} in tubular lumen, thereby lowering Ca^{2+} availability for stone formation. Hypocitraturia predisposes patients to calcium stones.

- Conditions associated with chronic metabolic acidosis such as RTA can reduce intraluminal citrate thus increased stone risk:
  - Citrate exists as a divalent (citrate^{2-}) or trivalent (citrate^{3-}) anion.
  - Citrate^{2-} + HCO_3^- → Citrate^{3-} + CO_2 + H_2O
  - In metabolic acidosis (ie, lack of HCO_3^-), there are more citrate^{2-} than citrate^{3-}. Proximal tubular reabsorption of citrate^{2-} occurs more readily than that of citrate^{3-}, leaving less citrate in tubular lumen to form *soluble* complexes with Ca^{2+}.
  - Intracellular acidosis associated with metabolic acidosis also promotes citrate mitochondrial uptake and metabolism, hence lower cytoplasmic concentration. This results in a more favorable chemical gradient for tubular citrate reabsorption, leaving less citrate in tubular lumen.
- Others: vitamin A deficiency (associated with reduced urinary concentration of stone inhibitors glycosaminoglycans and citrate and increased urinary calcium and oxalate excretion), hot climates, immobilization, urinary tract anomalies

Specific therapeutic considerations for calcium stones

- Consider medical therapy if a dietary trial of 3 to 6 months does not improve the urine chemical profile or if there is evidence of increasing stone formation (eg, an increase in the size and/or number of stones).
- For hypercalciuria:
  - Thiazide (watch for hypokalemia and treat as needed) with/without low-dose K^+-sparing diuretic amiloride to increase Ca^{2+} reabsorption. The inhibitory effect on sodium reabsorption by amiloride is thought to be via hyperpolarization of cell membrane, thereby promoting calcium entry into the cell via apical calcium channels. Avoid triamterene due to potential for intratubular crystallization.
  - If thiazide/amiloride intolerance:
    - Consider 30 to 60 mmol of K-HCO_3 or K-citrate daily in divided doses (bid to tid) if safely tolerated (ie, no hyperkalemia).

Alkalinization may improve citrate excretion. Avoid Na^+-alkali salts because Na^+ load increases urinary Ca^{2+} excretion.

- Must monitor urine pH and serum K^+ with K-salt alkalinization. Urine pH more than 7.0 may facilitate calcium phosphate precipitation.

- Administration of neutral orthophosphate reduces Ca^{2+} excretion and increases excretion of calcium stone inhibitors (pyrophosphate).
  - Example of neutral orthophosphates: K-phos neutral, 1.0 to 2.5 g/d in divided doses (bid-qid)
  - May be considered for hyperabsorptive hypercalciuria due to high $1,25(OH)_2D$ state because phosphate reduces $1,25(OH)_2D$ level and may also bind to intestinal calcium

- For enteric hyperoxaluria:
  - Low fat/oxalate diet if effective
  - Consider oral calcium carbonate or citrate (1-3 g daily) with meals to bind gut oxalate.
  - Cholestyramine binds both bile acids and oxalate, but its GI side effects may limit routine use.
  - Oral oxalate decarboxylase (reloxaliase) in enteric hyperoxaluria: Reloxaliase is an oral agent that can be taken with food to degrade oxalate—under Phase 3 trial.
- If hypocitraturia is present:
  - Consider fruit juice and/or K-citrate (monitor K level in patients with advanced CKD).
  - Urine alkalinization to increase urinary citrate levels

  Lumen $Citrate^{2-}$ + HCO_3^- (from alkalinization) $\rightarrow$ $Citrate^{3-}$ + CO_2 + H_2O. Reabsorption of $citrate^{3-}$ at PT (via Na-citrate cotransporter in luminal membrane) is lower than that for $citrate^{2-}$. The higher concentration of luminal citrate facilitates the formation of soluble calcium citrate complexes, thereby effectively reducing calcium availability for calcium stone formation.
  - Alkalinization also reduces intracellular citrate metabolism, resulting in higher intracellular citrate concentration. The higher

intracellular citrate concentration leads to less favorable chemical gradient for tubular citrate reabsorption, hence higher luminal citrate availability. **NOTE**: Hypokalemia induces intracellular acidosis and associated increased intracellular citrate metabolism, which leads to lowering of intracellular citrate levels and formation of a favorable chemical gradient for tubular citrate reabsorption.

- Magnesium supplement: Supplement only if serum magnesium is also low. Treatment with magnesium has not been shown to reduce stone recurrence.
- Allopurinol: Consider allopurinol if there is hyperuricosuria in the absence of hypercalciuria or hyperoxaluria in patients with calcium oxalate stones. The use of allopurinol in these patients has been shown to reduce the likelihood of calcium oxalate stone recurrence.

Uric acid stone

Risks for uric acid stones

- Low urine pH
- Defect in ammoniagenesis: NH_3 buffers urine pH. The lack of NH_3 results in low urine pH.
- Ketogenic diet
- Conditions associated with hyperuricosuria:
  - Purine overproduction: myeloproliferative disorder, acute leukemia, glycogen storage disease, malignancy
  - Metabolic syndrome, obesity, diabetes mellitus, insulin resistant
    - Excessive dietary acid ingestion and/or increased endogenous acid production
    - Defective NH_4^+ excretion
    - Absence of inhibitors or presence of promoters of uric acid precipitation

Management of uric acid stones

- Urine alkalinization, for example, K-citrate 10 to 20 mmol bid-tid

NOTE

Alkalinization of urine is the MOST important intervention for uric acid stone formers in addition to maintaining urine volume above 2.5 L/d. Urinary alkalinization with citrate is thought to be more important than reducing uricosuria.

- For uric acid stone formers who do not respond to alkali therapy, increase a morning dose or add a mid-day dose of alkali to prevent urinary pH fall that may occur late afternoon and evening.
- K-citrate is more effective in reducing calcium oxalate supersaturation than sodium bicarbonate. Sodium bicarbonate increases urine sodium excretion and associated urine calcium excretion, whereas K-citrate increases urinary K excretion and reduces urine calcium excretion.
- Reduction in uricosuria:
  - Xanthine oxidase inhibitors (eg, allopurinol, febuxostat) if overproduction of uric acid
  - Reduction of purine dietary intake with care to avoid malnutrition
- Reversal of metabolic syndrome if applicable/possible

Struvite, also known as triple phosphate stone

Composition: magnesium ammonium phosphate (struvite) and calcium carbonate-apatite. Also known as "triple phosphate": Phosphate is present in its trivalent form and combines with three cations: NH_4^+, Mg^{2+}, Ca^{2+}.

Pathogenesis and risks

- Urinary infection with urea splitting organisms (urease producing organisms): *Proteus, Hemophilus, Yersinia, Klebsiella, Serratia, Citrobacter, S. epidermidis, U. urealyticum, Pseudomonas*
- Associated with anatomical abnormalities, obstruction of pelviureteric junction, calyceal diverticulum, horseshoe kidney, tubular ectasia (medullary sponge kidney), ureterocele, vesicoureteral reflux, ureteral stricture

Management of struvite stones

- Treatment of underlying infections (culture specific)

- Stone removal: percutaneous nephrolithotomy (PNL) > combination shock-wave lithotripsy and percutaneous lithotomy > open surgery
- Provide 4 to 6 months of suppressive low-dose antibiotics (nitrofurantoin or sulfamethoxazole-trimethoprim)
- Medical therapy: urease inhibitor acetohydroxamic acid (Lithostat) 250 mg 3 to 4 times daily
  - Reserve for patients who cannot or refuse to undergo stone removal.
  - Inadequate urinary drug level if SCr above 2 mg/dL
  - Significant side effects (40%-60%): headaches, hemolytic anemia (15%-20%), depression, dyspepsia, diarrhea, hallucination, palpitations, sweating, deep vein thrombosis, pulmonary embolism
  - Mandatory follow-up of stone size in 3 to 4 months
- Correction of anatomical abnormality whenever possible

2,8-dihydroxyadenine (2,8-DHA) stone

Pathogenesis and manifestation

- Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of purine metabolism that leads to kidney stones and CKD.
- APRT deficiency prevents adenine recycling (from the purine nucleotide salvage pathway) and leads to adenine accumulation. Xanthine oxidase metabolizes the accumulated adenine to 2,8-DHA, which is insoluble in the urine and can cause kidney injury with or without stone formation.
- 2,8-DHA stone is radiolucent and may be mistaken for uric acid stone.

Management of 2,8-DHA stones

- Low-dose allopurinol or febuxostat with uptitration as needed for disappearance of 2,8-DHA crystals in the urine sediment has been suggested.
- Optimal dosing has not been defined.

Cystine stone

Causes of cystine stones/crystalluria

- Hereditary:
  - Mutation of renal epithelial cell transporters leads to reduced reabsorption of dibasic amino acids, including cysteine, ornithine, lysine, arginine (COLA). Cysteine dimerizes to form cystine, which is highly insoluble.
  - Genetic inheritance: predominantly autosomal recessive but may be autosomal dominant with incomplete penetrance
- Renal tubular immaturity in infants, Wilson disease, and Fanconi syndrome are other causes of elevated urinary cystine levels.

Clinical manifestations for patients with homozygous cystinuria

- Lifelong, recurrent urolithiasis that is difficult to manage surgically or medically.
- Greater than 50% of asymptomatic homozygotes develop kidney stones.
- Seventy five percent present with bilateral calculi.
- Typical age of onset: second or third decade of life; 25% in first decade; 30% to 40% in teenage years

Management of cystine stone

- High fluid intake 3.5 to 5.0 L/d. Note this is much higher than that required other types of stones. Monitor for hyponatremia.
- Alkalinization of urine with 40 to 80 mmol of K-citrate daily (urine pH >7.0)
- Reduction of sodium and protein intake to reduce urinary cysteine excretion
- Last resort: Use thiol-containing drugs that can form heterodimers with cysteine, thereby competing for cysteine-cysteine disulfide bond formation, the insoluble cystine.
  - D-Penicillamine
  - α-Mercaptopropionylglycine (tiopronin)

- Both D-penicillamine and tiopronin have significant side effects, which include loss of taste, fever, proteinuria, serum sickness-type reactions, and nephrotic syndrome.

Drug-Associated Stones, Urinary Crystallizations

Calcium stone formation: loop diuretics (increase urinary calcium excretion); vitamin D (GI absorption of calcium); glucocorticoids (bone resorption); calcium-containing antacids; theophylline (interferes with pyridoxine metabolism and worsens oxaluria in primary oxaluria type 1); acetazolamide (alkalinize urine, increase risk for calcium phosphate stones), topiramate (antiepileptic, has significant carbonic anhydrase activity thus alkalinization of urine), amphotericin B (alkalinize urine due to H^+-back leak), high-dose (ie, ≫500 mg/d) vitamin C (metabolized to oxalate)

Uric acid stone formation: probenecid

Medications that may crystallize: triamterene, acyclovir (high intravenous dose, eg, treatment dose for encephalitis), indinavir, allopurinol (xanthine stones)

Stone Diagnosis

Imaging studies

Ultrasound (US) versus noncontrast computed tomography (CT)

- CT has a sensitivity of 97% and specificity of 98% to 99% in detecting stones.
- Ultrasound may miss ureteral stones less than 3 mm.
- Cost, availability
- Radiation exposure is high with CT.
- Contrast-enhanced CT may be required to diagnose indinavir stones.

Plain film (Kidney-Ureter-Bladder x-ray, KUB)

- Detects radiopaque stones (eg, calcium-containing, struvite, cystine)

- Detects stones more than 5 mm
- Low dose of radiation
- Inexpensive

Magnetic resonance imaging: poor tool for visualizing stones
Intravenous pyelogram: contrast dye exposure

NOTE

- Radiolucent "stones" on plain x-ray film:
  - Uric acid and xanthine stones
  - 2,8-DHA stone
  - Case report of pseudoephedrine/guaifenesin stone
- Cystine and struvite stones are often but not always radiopaque.
- Staghorn-appearing stones are typically seen with struvite stone, but they may be seen in other stone types: struvite (triple phosphate, magnesium ammonium phosphate) ≫ calcium carbonate-apatite > cystine, uric acid stones

Biochemical evaluation

First-time uncomplicated stone presentation

- Basic chemistry, serum calcium, phosphorus, uric acid
- Routine urinalysis
- Consider: 24-hour urine for volume, creatinine, pH, calcium, oxalate, citrate, uric acid
- Complete metabolic profile evaluation, outlined later, is optional.

Indications for complete metabolic profile evaluation

- Recurrent stone or bilateral stone disease
- Family history of stones
- Presence of inflammatory bowel disease, malabsorption
- Past medical history with any of gout, RTA, pHPT, osteoporosis or pathologic skeletal fractures, nephrocalcinosis, or bariatric surgery
- Struvite, cystine, uric acid, or calcium phosphate
- Patient is a child.

Complete metabolic profile evaluation

- Analysis of stone composition if available

- Two 24-hour urine collections (one during usual daily activities and diet, ie, work-day, and one during resting day, ie, weekend to evaluate for work-related factors) for: volume, creatinine (to determine collection adequacy), pH (hint to type of stone), Na^+ (relevant in calcium stones), stone substrates: Ca^{2+}, oxalate, uric acid, cystine (if young age or strong family history of cystine stones), ammonium, stone inhibitors: citrate, Mg^{2+}, K^+, dietary protein intake: SO_4^{2-} (high content of sulfate-containing amino acids reflects animal protein intake), urea nitrogen
- Laboratory calculations of urinary supersaturation of stone substrates if available
- Serum: full chemistry panel (eg, Chem 10 panel), uric acid
- If serum calcium is high or high normal, obtain PTH, $1,25(OH)_2D$, chest x-ray (sarcoidosis). Consider urine evaluation for mycobacterium tuberculosis in endemic areas.

Management of Kidney Stones: General Consideration

Spontaneous stone passage depends on stone location and stone size.

- Stone location: Proximal stones are less likely than distal stones to pass spontaneously.
- Stone size:
  - Less than 5 mm, spontaneous passing rate up to 95%
  - Around 5 to 8 mm, spontaneous passing rate 60% to 70%
  - Greater than 8 mm, spontaneous passing rate approximately 10% to 20%

Pain control

- NSAIDS if no volume depletion, kidney disease, GI bleed, or contraindications:
  - Low cost
  - Inhibit prostaglandin-mediated pain pathways
  - Decrease ureteral contractility

    - Stop NSAIDs at least 3 days prior to shock-wave lithotripsy to minimize bleeding risks.
- Otherwise use opioids: faster onset of pain relief compared with NSAIDs but concerns for abuse potential
- Combination of NSAIDs and opioids may be considered.

Urologic Management Options

Small stones less than 10 mm

- Observation if pain is controlled and no evidence of obstruction or infection
- Initiate medical expulsion therapy (MET) below for ureteral stone.

Medical expulsion therapy

- Up to 4 to 6 weeks trial of α-blockers (eg, tamsulosin) or CCB, (eg, nifedipine only if hypertensive) with/without low-dose glucocorticoid (eg, prednisone 20-25 mg daily × 10 days)
- Rationale for α-blockers:
    - Inhibit basal ureteral tone and peristaltic frequency and decrease intensity of ureteral contractions, thereby facilitating stone passage
    - Slightly faster stone passage compared with CCB

Urology consults if MET fails

Extracorporeal shock-wave lithotripsy

- May be used for small stones that do not pass
- Has been linked to a small risk of HTN
- Does not work well for larger stones, lower pole stones, or individuals who are obese
- Contraindications: coagulopathy, pregnancy, untreated urinary tract infection, distal obstruction, adjacent arterial aneurysm

Ureteroscopy (URS)

- Has better stone clearance compared with SWL

- May be used for upper tract stones
- Has higher complication risks than SWL

Percutaneous nephrolithotomy

- Has best stone clearance compared with URS and SWL
- Recommended for stone size more than 2 cm or complex renal anatomy, lower pole stones more than 1 cm, staghorn stones, *or stones unsuccessfully managed by SWL or US*.

Indications for urgent urologic consult

- Presence of infection with urinary tract obstruction
- Urosepsis
- Intractable pain or vomiting, or both
- Acute kidney failure
- Obstruction in solitary or transplanted kidney
- Bilateral obstructing stones

Monitoring Response

- A 24-hour urine collection after 6 to 8 weeks for chemical profile, pH, and volume. Of note, follow-up measurements of urine calcium level may NOT be a reliable predictor of treatment effectiveness for reducing stone recurrence risk. Increased fluid intake, however, has been shown to significantly reduce risk of stone recurrence over 5-year follow-up.
- Imaging studies: helical CT or ultrasound at 1 year. If negative, repeat in 2 to 4 years depending on findings and risks.

CHAPTER 4

Chronic Kidney Disease

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ASSESSMENT OF CHRONIC KIDNEY DISEASE (CKD)

Background

In assessing CKD, the cause of CKD based on clinical context, personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and genetic and pathologic diagnosis needs to be established.

CKD definition (Kidney Disease Improving Global Outcomes [KDIGO])

CKD is defined as having either structural or functional abnormalities of the kidneys, of 3 months or more in duration, with implications for health. **Structural abnormalities** of the kidney refer to either pathologic abnormalities on biopsy or imaging or markers of kidney damage, including abnormalities in the composition of the blood or urine (eg, may include abnormal serum or urine markers of tubular or glomerular dysfunction).

Functional abnormality of the kidney refers to having glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 with or without underlying kidney damage (eg, hepatorenal or cardiorenal syndrome causing dysfunction related to decreased renal perfusion and may not be associated with fixed kidney damage).

Chronicity is defined as a duration of 3 months or more or evidence of chronicity, for example, findings on imaging of decreased kidney size, atrophy, and loss of cortical definition;

presence of chronically low GFR; and finding on biopsy of tubular atrophy and tubulointerstitial fibrosis. Chronicity should not be based on a single abnormal estimated GFR (eGFR) or urine albumin-to-creatinine ratio (ACR) because they may reflect a recent acute kidney injury (AKI) event.

CKD classification

CKD staging is based on eGFR category (G1-G5) and albuminuria category (A1-A3) (**Table 4.1**).

Table 4.1 KDIGO classification of CKD stages according to eGFR and albuminuria

eGFR (mL/min/1.73 m^2)	Albuminuria Spot urine albumin:creatinine ratio		
	A1 **<30 mg/g Cr**	**A2** **30-300 mg/g Cr**	**A3** **>300 mg/g Cr**
G1: ≥90	No CKD	G1 A2	G1 A3
G2: 60-89	No CKD	G2 A2	G2 A3
G3a: 45-59	G3a A1	G3a A2	G3a A3
G3b: 30-44	G3b A1	G3b A2	G3b A3
G4: 15-29	G4 A1	G4 A2	G4 A3
G5: <15	G5 A1	G5 A2	G5 A3

Increasing risk → (right)

Increasing risk → (bottom)

CKD epidemiology

- In 2017, a systematic analysis from the all-age global burden of CKD project revealed approximately 698 million cases of all-stage CKD.
- In 2021, a joint statement from the American Society of Nephrology, European Renal Association, and International Society of Nephrology revealed that more than 850 million people suffer from kidney disease, which is approximately:
  - 2 times the number of people who live with diabetes
  - 20 times the number of people with cancer, and

    - 23 times the number of people with acquired immunodeficiency syndrome
- CKD led to an estimate of 2.6 million deaths in 2017 and ranked 11th among the leading causes of death between 1990 and 2019. This rise in rank is attributed to aging and increasing burden of risks for CKD (eg, diabetes and hypertension [HTN]).
- Overall lifetime risks for CKD stages 3a, 3b, and 4 and end-stage kidney disease (ESKD) in the United States have been reported to be 59.1%, 33.6%, 11.5%, and 3.6%, respectively.
- Women have greater CKD risk, but lower ESKD risk compared to men.
- Lifetime risks of CKD stages 4 and 5 and ESKD were higher in Blacks and developed 10 to 15 years earlier than in Whites.
- Diabetes mellitus (DM) is the leading cause of CKD in developed and many developing countries.

Glomerular Filtration Rate (GFR)

Measured GFR (mGFR)

- GFR may be measured as the clearance rate of any solute that is 100% filtered.
- Clearance of any solute "*S*" equals $[U_S] \times V \div [P_S]$, where $[U_S]$ and $[P_S]$ represent the concentrations of solute "*S*" in the urine and plasma, respectively, and V represents urine volume per unit time.
- The ideal solute for the calculation of GFR should be:
    - Naturally made (endogenous) in the plasma
    - 100% freely filtered by the glomerulus
    - Not secreted by renal tubules
    - Not reabsorbed by renal tubules

Creatinine as a solute to measure GFR

Traditionally, creatinine has been used as the "solute" of choice in estimating GFR because the kidney freely filters creatinine.

$$\text{GFR} \approx \frac{[\text{urine creatinine concentration}] \times \text{urine output rate}}{[\text{plasma creatinine concentration}]}$$

Limitations of using creatinine as a solute to measure GFR

- Creatinine level reflects muscle mass and dietary intake.
- Creatinine levels are typically in the low-normal range for older patients or patients with malnutrition, limb amputation(s), or cirrhosis (reduced hepatic creatinine synthesis, dilution due to volume overload). Creatinine levels may be in the high-normal range despite having normal GFR in muscular young individuals.
- Creatinine is secreted by renal tubules, which leads to overestimation of GFR.
- A solute that is both filtered by the glomerulus and secreted by renal tubules (eg, creatinine) will overestimate the GFR, since there will be more solute in the urine than if the solute comes from filtration alone. In addition, tubular creatinine secretion is upregulated in advanced CKD, which can further overestimate GFR in this patient population.
- Drugs that inhibit proximal tubular secretion of creatinine and affect mGFR include cimetidine, dronedarone (antiarrhythmic), trimethoprim, probenecid, pyrimethamine, salicylates, dolutegravir, cobicistat, ranolazine, tyrosine kinase inhibitors (including imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, pazopanib), and poly-ADP ribose polymerase inhibitors (eg, olaparib, rucaparib).
- Serum creatinine (SCr) may increase after a large, cooked meat or fish meal (creatine from meats is converted to creatinine with heat). One study reported an increase in approximately 20 µmol/L (0.23 mg/dL). When using SCr to assess GFR, wait at least 12 hours to measure SCr following meat or fish intake.

Blood urea nitrogen (BUN) as a solute to measure GFR

- A solute that is both filtered by the glomerulus and reabsorbed by the tubules (eg, BUN) will underestimate the GFR, since less

solute will end up in the urine.

- For the reasons above, GFR estimates from 24-hour urine collections in advanced CKD may be calculated as the average of creatinine and urea clearances.
- Creatinine and urea clearances require a 24-hour urine collection and can be cumbersome.

The use of cystatin c to assess GFR

- Cystatin c is a cationic low-molecular-weight (LMW) cysteine proteinase inhibitor that is produced at a constant rate by all nucleated cells. It is 99% filtered by glomerulus and metabolized by proximal tubular cells and returned to the serum as amino acids. Very little is excreted in the urine. The latter prevents the use of cystatin c to directly measure 24-hour clearance.
- Serum cystatin c (SCys) level reflects GFR well.
- Normal cystatin c range:
  - Both males and females: age 20 to 50: 0.70 to 1.21 mg/L; age greater than 50: 0.84 to 1.55 mg/L
  - Young healthy individuals: 0.53 to 0.95 mg/L

Advantages of using SCys compared to SCr

- Cystatin c may more accurately estimate GFR than SCr in patients with reduced muscle mass (eg, liver disease, neuromuscular disease).
- Cystatin c may detect AKI earlier than SCr.
- Cystatin c has been reported to be a better predictor of deaths from cardiovascular (CV) causes and CKD complications. Whereas cystatin c correlates linearly with CV risk (eg, heart failure [HF]), SCr correlates in a J-curve relationship.

Limitations of using SCys

- Cystatin c production and metabolism may be altered in various clinical conditions. Higher SCys may be seen with older age, male gender, White race, greater height and weight, higher lean body mass or fat mass, diabetes, inflammatory state, and lower serum albumin level. Other factors that may alter SCys include thyroid

disease (hypo- or hyperthyroid), malignancy, and use of glucocorticoids.

- Cystatin c level may also vary by race.
- Unless combined with SCr, eGFR formulas with cystatin c alone are not more accurate in estimating GFR or predicting ESKD.
- While cystatin c-alone–based eGFR appears to be a better biomarker for mortality and CKD complications, SCr-based eGFR serves as a better predictor of ESKD. This is thought to be due to the non-GFR determinants of SCys level, such as inflammation and vascular remodeling.

The use of exogenous radioisotopes to measure GFR (mGFR)

- Radioisotopes of inulin, iothalamate, iohexol, ethylenediaminetetraacetic acid (EDTA), and diethylenetriaminepentaacetic acid (DTPA) are freely filtered by glomeruli and can be used to measure GFR with nuclear scanning.
- GFR may be measured as urinary or plasma clearance of an exogenous marker.
  - Urinary clearance can be measured using inulin, iothalamate, or iohexol. Measurement of urinary clearance requires a constant infusion to maintain a constant level of the radioisotope over 3 to 4 hours. After achieving equilibrium, timed urinary and plasma radioisotope concentrations are measured to calculate urinary clearance.
  - Plasma clearance can be measured using ^{51}Cr-EDTA or iohexol.
- Special considerations regarding mGFR:
  - In clinical settings where treatment decisions are based on GFR, mGFR is suggested.
  - Urinary clearance is preferred to plasma clearance in individuals with extensive edema.
  - If radioisotopes are not available, use timed 24-hour urine creatinine clearance (CrCl). Monitor urine collection adequacy and measure SCr 12-hour after meat or fish meal.

Equations to estimate GFR (eGFR)

Cockcroft-Gault (CG) formula (dependent variables: age, gender, weight, SCr)

- Male: CrCl (mL/min) = ([140 − age] × weight [kg]) ÷ (72 × SCr [mg/dL])
- Female: same as formula for male above × 0.85 (empirical correction factor for presumed lower muscle mass in females)
- Note CG formula is in mL/min. To normalize to 1.73 m^2 body surface area (BSA), multiply CrCl above by the ratio (1.73/patient's BSA).

Limitations of CG formula

- CrCl is overestimated in patients with excessive weight due to adipose tissue or volume (weight is in the numerator).
- eGFR is likely to be overestimated because it is based on CrCl, not true GFR. Tubular creatinine secretion is not accounted for.
- Derivation of CG formula was based on old methods of SCr measurement and may not be accurate with modern SCr measurements.
- Traditionally, CG formula has been used for drug dosing. With modern SCr measurements and new eGFR equations, clinicians must read package inserts for recommended methods of eGFR used to determine renal dose adjustments.

Chronic kidney disease epidemiology collaboration (CKD-EPI)

2009 CKD-EPI

- Derived from a large database involving participants with diverse characteristics including those with and without CKD, DM, and known organ transplantation
- Dependent variables: age, gender, White or Black race, SCr
- Derived based on either SCr-alone CKD-EPI(cr), cystatin c (cys)-alone CKD-EPI(cys), or both SCr and cystatin c CKD-EPI(cr-cys).

For CKD-EPI(cr-cys), both SCr and SCys should be measured from the same blood sample.

CKD-EPI(cr) versus CKD-EPI(cys), versus CKD-EPI(cr-cys)

- Compared to CKD-EPI(cr), CKD-EPI(cys) is not more accurate in estimating GFR, but is more accurate in estimating GFR in patients with low body mass index (BMI) and risk predictions.
- Compared to either CKD-EPI(cr) or CKD-EPI(cys) alone, combined CKD-EPI(cr-cys) is generally more accurate for estimating GFR.

2021 CKD-EPI

- 2021 CKD-EPI is derived from the original CKD-EPI database but excludes race.
- Compared with the 2009 CKD-EPI(cr) equation, 2021 CKD-EPI underestimates GFR in Black individuals and overestimates GFR in other individuals. 2021 CKD-EPI(cr-cys) equation attenuates these differences.

See **Appendix A4.1** for other equations used to estimate GFR.

KDIGO 2024 recommendations (Kidney International 2024)

- In adults at risk for CKD, the use of creatinine-based eGFR is recommended.
- If cystatin c is available, the GFR category should be estimated from the combination of creatinine and cystatin c–based eGFR equation.
- Clinical laboratories should:
  - Measure SCr using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope dilutional mass spectrometry (IDMS) reference methodology.
  - Report eGFR in adults using the CKD-EPI equation.
- Racial ethnic and regional modifications to CKD-EPI creatinine equations are required.
- In adults with eGFR(Cr) of 45 to 59 mL/min/1.73 m^2 who have no other markers of kidney damage and confirmation is required,

cystatin c measurement is suggested. If eGFR(cys) or eGFR(Cr-cys) is also less than 60 mL/min/1.73 m^2, the diagnosis of CKD is confirmed.

- Note that all eGFR formulas are less accurate in non–steady state.

In terms of preferred equations to use

CKD-EPI(cys) is suggested for the following (due to the presence of non-GFR determinants of SCr).

- Anorexia nervosa
- Extreme sport, bodybuilders
- Above-knee amputation
- Para- or quadriplegia/paresis
- Muscle wasting diseases
- Use of medications that affect tubular secretion of creatinine
- Dietary factors: low-protein, keto-, vegetarian, or high-protein diets or creatine supplements

CKD-EPI(cr) is suggested for the following (due to unknown non-GFR determinants of SCys):

Smoking if no non-GFR determinants of SCr or comorbid illness

CKD-EPI(cr-cys) is suggested for the following (due to the presence of non-GFR determinants of both SCr and serum cystatin).

- Class III obesity (eg, BMI >40 kg/m^2)
- Malnutrition
- Above-knee amputation with comorbid illness
- Para- or quadriplegia/paresis or muscle wasting diseases with comorbid illness
- Cancers or chronic illness (although there is a likelihood of lower accuracy among frail individuals and those with cancers with high cell turnover)
- Use of anabolic steroids (effects on SCys is not known)

- CKD-EPI(cr-cys) is highly inaccurate in HF and cirrhosis and may be inaccurate in catabolic-consuming diseases (eg, tuberculosis [TB], acquired immune deficiency syndrome, hematologic malignancies, severe skin disease) but may be used for routine evaluation of GFR.

mGFR is suggested for the following conditions if treatment decisions will be based on the level of GFR:

- Malnutrition
- Cancers or chronic illness or catabolic-consuming disease
- HF
- Cirrhosis
- Catabolic-consuming diseases
- Use of medications that decrease tubular secretion of creatinine
- GFR measurement using an exogenous filtration marker (eg, radioisotopes) is suggested under circumstances where more accurate ascertainment of GFR will impact treatment decisions (eg, kidney donation).

Sex and gender consideration for eGFR

- Gender-affirming testosterone therapy is associated with increased SCr.
- Effect of estrogen therapy on SCr is less certain.
- Use of eGFR(cys) may reduce challenges associated with eGFR(cr).

Categorization of eGFR

- G1: normal or high eGFR 90 mL/min/1.73 m^2 or more
- G2: mildly decreased eGFR 60 to 89 mL/min/1.73 m^2
- G3a: mildly to moderately decreased eGFR 45 to 59 mL/min/1.73 m^2
- G3b: moderately to severely decreased eGFR 30 to 44 mL/min/1.73 m^2
- G4: severely decreased eGFR 15 to 29 mL/min/1.73 m^2

- G5: kidney failure eGFR less than 15 mL/min/1.73 m^2
- G5D: The letter D denotes dialysis dependent.
- G1-5T: The letter T denotes kidney transplant.

Proteinuria

- Urinary protein consists of LMW proteins, albumin, immunoglobulins, and Tamm-Horsfall proteins, among others. LMW proteins and small amounts of higher molecular weight proteins can be filtered by the glomerulus, then nearly completely reabsorbed and metabolized by renal tubules in the normal kidney.
- Normal degree of proteinuria is generally less than 150 to 200 mg/d (or <0.2 g/g creatinine) but may be up to 250 to 300 mg/d (or ≤0.3 g/g creatinine) in normal pregnancy due to hyperfiltration.
- Measurement of spot urine protein-to-creatinine (uPCR) and spot ACR ratios should be ideally done in the morning first-void, mid-stream sample because:
  - First-void morning samples correlate well with 24-hour urine collection.
  - There is relatively low intraindividual variability with first-void morning samples.
  - Morning uPCR is required to exclude orthostatic (postural) proteinuria.
  - uPCR may not correlate with 24-hour urine collection in situations of oliguria or if renal function is not stable.
- Proteinuria may be categorized as tubular (resulting from impaired tubular reabsorption), glomerular (resulting from abnormalities in protein filtration in the glomerulus), or overflow due to paraproteinemia (monoclonal gammopathy).

Tubular proteinuria

- Can be seen with acute tubular injury, tubulointerstitial diseases
- LMW proteins are not only easily filtered but also readily reabsorbed by proximal tubules. Proximal tubular injury leads to the loss of LMW proteins.
- Tubular proteinuria is typically less than 1 to 2 g/d (or 1 to 2 g/g creatinine) and composed of predominantly LMW protein, NOT albumin.

Glomerular proteinuria

- Proteinuria associated with glomerular injury (ie, glomerular diseases) varies in range depending on the type of injury (nephrotic vs nephritic glomerular disease).
- Glomerular proteinuria predominantly composed of albumin.
- Albuminuria may be classified as:
  - A1: normal to mildly increased albuminuria: albumin excretion rate (AER) less than 30 mg/24 h or ACR less than 30 mg/g of creatinine (Cr)
  - A2: moderately increased: AER 30 to 300 mg/24 h or ACR 30 to 300 mg/g Cr
  - A3: severely increased: AER greater than 300 mg/24 h or ACR greater than 300 mg/g Cr
- Factors that may alter urine ACR:
  - Red blood cells (RBCs) in urine, exercise, urinary infection (proteins produced from organisms) may cause falsely elevated ACR.
  - Conditions that can change urinary creatinine concentration can change ACR (eg, high-protein intake or muscular individuals can have increased urine Cr and result in a falsely lower ACR; frail or older individuals with lower urine Cr may have exaggerated ACR).
- The degree of albuminuria has been shown to have a strong relationship with both kidney and cardiovascular disease (CVD) risks even at very low levels.

Overflow proteinuria due to paraproteinemia

- The high production and glomerular filtration of LMW paraproteins (eg, light chains with multiple myeloma) overwhelm the proximal tubular reabsorptive capacity and lead to proteinuria. This form of proteinuria is called "overflow proteinuria."
- The degree of overflow proteinuria depends on the amount of light chains produced and filtered. Albuminuria may be present if there is concurrent glomerular basement membrane (GBM) injury due to paraprotein or associated amyloid depositions.

Methods to assess proteinuria

- Routine urinalysis (RUA) dipstick detects predominantly albuminuria based on its ability to change pH.
- RUA does not detect tubular proteins or light-chain immunoglobulins well.
- Semiquantitative assessment of proteinuria on RUA is affected by urinary concentration.
- 24-Hour urine collection detects all types of proteins but can be cumbersome to collect. Confirmation of collection adequacy requires measurement of creatinine in the 24-hour specimen. Total creatinine in the 24-hour collection should be approximately 15 to 20 mg/kg/d of creatinine for females and 20 to 25 mg/kg/d for males if accurately collected.
- uPCR detects all types of proteins and reduces variations due to hydration status. It may be expressed as µg/mg Cr, mg/g Cr, g/g Cr, or mg/mmol Cr. For newly diagnosed CKD, obtain either uPCR or 24-hour urine collection to quantify total proteinuria.

NOTE

- Proteinuria composed of less than 25% albuminuria may suggest either the presence of LMW proteins due to tubular injury and/or overflow proteinuria from monoclonal gammopathy.
- Significant proteinuria mismatch (ie, high degree of proteinuria from either uPCR or 24-hour collection in association with minimal proteinuria from RUA) suggests

the presence of free light chains (Bence Jones protein).

- "Selectivity of proteinuria" refers to the ratio of clearance of immunoglobulin G (IgG) (molecular weight of 160,000 Da) to that of transferrin (88,000 Da). A value of less than 0.1 indicates highly selective proteinuria and suggests the diagnosis of minimal change disease in children and predicts corticosteroid responsiveness.

General Facts Regarding CKD

The following data were obtained from the U.S. Department of Health and Human Services, National Institute of Diabetes and Digestive and Kidney Diseases: Kidney disease statistics for the United States.

Epidemiology

- CKD affects more than one in seven adults in the United States (~37 million Americans).
- It is estimated that 9 out of 10 adults with CKD are not aware that they have CKD.
- The two most common causes of kidney disease in the United States are from DM and HTN.
- According to the United States Renal Data System (USRDS) 2020 Annual Data Report:
  - 808,000 individuals have ESKD, with 69% on dialysis and 31% with a kidney transplant.
  - Although CKD is slightly more common in women (14%) than in men (12%), men are 1.6 times more likely to develop ESKD than women.
  - Racial differences compared with Caucasians:
    - Blacks are 4 times more likely to develop ESKD.
    - Blacks make up 13% of the total population but account for 30% of all ESKD.
    - Blacks are more likely to have ESKD caused by HTN than Caucasians or Hispanics.

    - Hispanics and Native Americans are more than 2 times more likely to develop ESKD.
    - Asians are 1.4 times more likely to develop ESKD.
- Among patients with ESKD who were initially waitlisted for a kidney transplant in 2015, more than half (55.7%) received a kidney transplant by the end of 5 years.

Medicare spending

According to the USRDS 2022 Annual Data Report:

- Medicare spending for beneficiaries with CKD (not including ESKD) ages greater than 66 exceeded $75 billion in 2020, representing 25.2% of Medicare spending in this age group.
- Medicare spending for beneficiaries with ESKD was $50.8 billion in 2020.

Mortality (USRDS 2022 Annual Data Report)

- In 2020, the adjusted mortality rate among Medicare beneficiaries ages greater than 66 years with CKD (103.9/1,000 person-years) was greater than twice that of beneficiaries without CKD (47.9/1,000).
- Adjusted mortality in patients with ESKD decreased between 2010 (151.6/1,000) and 2019 (129.1/1,000) before abruptly increasing in 2020 (152.1/1,000). Adjusted mortality rates among patients with ESKD from 2019 to 2020:
    - In patients receiving hemodialysis (HD), adjusted mortality increased by nearly 17%.
    - In patients receiving peritoneal dialysis (PD), adjusted mortality increased by 20%.
    - In patients with a kidney transplant, adjusted mortality increased by 33%.

RISK ASSESSMENT OF CKD (KDIGO 2024)

Suggested Monitoring Frequency of GFR and Albuminuria

- Annual monitoring for CKD G1 to G2; biannual for CKD G3; quarterly for CKD G4; every 6 weeks for CKD G5
- Increase monitoring frequency among individuals with high risk of progression (eg, higher level of albuminuria, changing clinical conditions or therapeutic interventions)

Predictors of CKD Progression

- KDIGO: In predicting risk for outcome of CKD, identify (1) cause of CKD, (2) GFR category, (3) albuminuria category, and (4) other risk factors and comorbid conditions.
- See **Appendix A4.2** for angiotensin II (Ang II) and proteinuria as contributors of CKD progression.

GFR and albuminuria changes that warrant evaluation

- A reduction in eGFR of more than 20% on a follow-up test warrants evaluation.
- A reduction in eGFR of more than 30% following hemodynamically active therapies (eg, addition of angiotensin-converting enzyme inhibitor [ACEi], angiotensin receptor blocker [ARB], or sodium glucose cotransporter-2 inhibitor [SGLT2i] warrants evaluation. A reduction of less than 20% to 30% may be expected and is generally transient. This lower level of eGFR reduction is thought to provide long-term cardiac and kidney protective effects. Reflexive discontinuation of these cardioprotective and kidney protective agents should be avoided. However, close monitoring to ensure no further reduction in eGFR is warranted.
- Doubling of ACR at a subsequent visit warrants evaluation.
- Rapid progression of CKD is defined as a sustained eGFR decline by greater than 5 mL/min/1.73 m^2/y.

Key Predictors of CKD progression

- Estimate absolute risk of kidney failure in individuals with CKD G3 to G5 using an externally validated risk equation (eg, online calculators from CKD Prognosis Consortium: Risk Models) is suggested to assess future risks for kidney failure and CV complications and mortality, and management planning.
- **Kidney failure risk calculator (online at CKD Prognosis Consortium):** The kidney failure risk equations were developed in patients with CKD stages G3 to G5 referred to nephrologists in Canada and have been validated in greater than 1 million individuals and greater than 1 million events, spanning 30+ countries worldwide. The equations accurately predict the 2- and 5-year probability of treated kidney failure (dialysis or transplantation) for a potential patient with CKD stages 3 to 5. Calculated risk is based on patient's age, sex, eGFR, and ACR (four-variable equation) with or without calcium, phosphate, bicarbonate, and albumin (eight-variable equation).
- **Tangri calculator (online at CKD Prognosis Consortium: Advanced CKD Risk Tool)** has been shown to accurately predict 2- and 5-year kidney failure risks as well as nonfatal CV events and death risk for adults with eGFR less than 60 mL/min/173 m^2. Calculated risk is based on patient's age, gender, race (Black on White), eGFR, systolic blood pressure (SBP), history of CVD, DM, ACR, and smoking history.
- **Disease-specific prediction equations** are available and should be used for immunoglobulin A (IgA) nephropathy (International IgA Nephropathy Prediction Tool [IIgAN-PT]) and autosomal dominant polycystic kidney disease (Mayo Clinic Classification tool and Predicting Renal Outcome in Polycystic Kidney Disease [ProPKD] score).
- **5-year kidney failure risk of 3% to 5%:** referral criteria for nephrology services in areas with limited access to nephrology care
- **2-year kidney failure risk of more than 10%:** time for multidisciplinary care in addition to eGFR-based criteria and other

clinical considerations

- **2-year kidney failure risk of more than 40%:** time for modality education, preparation for kidney replacement therapy (KRT) (eg, vascular access planning or referral for transplantation)

Predictors of CV and mortality risks in patients with CKD

- Predictor calculators can be found at ckdpc.org/risk-models.html.
- For risk prediction of CV events, use models that include eGFR and albuminuria (ckdpc.org/risk-models.html).
- For mortality risk prediction to guide goal-of-care discussions, use models that predict all-cause mortality developed specifically for patients with CKD.

SLOWING CKD PROGRESSION AND MANAGING CV COMPLICATIONS

The management of CKD involves a multifaceted management plan that includes optimizing a healthy lifestyle and the use of medical therapies with proven benefits to both slowing CKD progression and reducing CV complications and mortality (**Table 4.2**).

Table 4.2 KDIGO: "Holistic approach to chronic kidney disease (CKD) treatment and risk modification"

Maintain healthy lifestyle	• **Maintain** healthy diet, physical activity, weight management, smoking cessation
First-line therapy	• **SGLT2** until dialysis or transplant • **Control systolic blood pressure** <**120 mm Hg** (use maximum dose of RASi as safely tolerated) • **Statin-based** therapy based on age and ASCVD (see text)
Targeted therapies	• **Glucose control** • Control glucose in patients with DM per guideline including the use of **GLP-1 RA** where indicated • **nsMRA**: Add an **nsMRA (finerenone)** to an SGLT2i as safely tolerated in individuals with T2D and CKD (eGFR >25 mL/min/1.73

	m^2) with albuminuria >30 mg/g Cr despite being on maximally tolerated dose of ACEi or ARB. • **Blood pressure control** • Add medications other than RASi to achieve SBP control (eg, calcium channel blockers, diuretics). • For resistant HTN, add **sMRA** as safely tolerated. • **Cardiovascular protection** • Antiplatelet based for clinical ASCVD • Add **ezetimibe** or **PCSK9** based on ASCVD and lipids. • Manage atrial fibrillation and ASCVD as for individuals without CKD.
Manage CKD complications	• **Manage** anemia, CKD-MBD, metabolic acidosis, hyperkalemia, and others

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKD-MBD, metabolic bone disorders associated with CKD; DM, diabetes mellitus; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MRA, mineralocorticoid receptor antagonist; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9, proprotein convertase subtilisin/kexin type 9; RASi, renin-angiotensin system inhibitor (ie, ACEi, ARB); SGLT2i, sodium glucose cotransporter-2 inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist.

Adapted from Rossing P, Caramori ML, Chan JCN, et al. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2022;102:S1-S127, with permission from Elsevier.

Suggested treatment recommendations and goals are based on KDOQI 2024.

Lifestyle: Healthy Diet, Physical Activity, Stop Tobacco Products, and Weight Management

Healthy diet

General: Encourage higher plant-based rather than animal-based food consumption; avoid ultra-processed foods; consider nutritional consult for CKD safe diet to avoid malnutrition.

Protein

- Rationale for low-protein diet: Low-protein diet can reduce uremic toxin generation and uremia and lower intraglomerular filtration pressure via afferent arteriolar vasoconstriction.
- Maintain protein intake of 0.8 g/kg/d in adults with CKD G3 to G5 not at risk for malnutrition.
- A very low-protein diet (0.3-0.4 g/kg body weight/d) supplemented with essential amino acids or ketoacid analogs (up to 0.6 g/kg body weight/d) may be considered in adults with CKD who are at risk for kidney failure and who are willing and able to follow such diet.
- Avoid protein intake of greater than 1.3 g/kg/d in adults with CKD at risk for progression.
- Plant-based proteins can reduce dietary acid load and are less likely to be associated with glomerular hyperfiltration than animal proteins.

Sodium

- Limit Na intake to less than 2 g/d (<90 mmol/d); equivalent to about one-third of a teaspoon of salt.
- In randomized controlled trials (RCTs) with up to 36-week follow-up, reduction in dietary Na has been shown to lower BP and risk of CV events in the general population and reduce albuminuria in individuals with CKD.

Physical activity: moderate intensity, for example, 150 min/wk or higher or as safely tolerated per CV and physical tolerance

Stop tobacco products: Enroll in smoking cessation programs if applicable and necessary. Tobacco smoking is not associated with CKD progression but with all-cause mortality.

Weight management: BMI greater than 25 kg/m^2 is associated with multiple chronic diseases and CKD.

Management of HTN

BP control can reduce CKD progression and reduce CV risk. CV risk reduction can occur beyond the benefit of BP control with specific drugs.

Goal: Achieving goal SBP less than 120 mm Hg using standardized office BP measurement *as safely tolerated* is suggested in individuals with CKD and HTN (KDIGO 2024).

Renin-angiotensin system inhibitors (RASi): ACEi or ARB

Beneficial effects of RASi beyond those of BP control

- Reduce glomerular pressure, hyperfiltration
- Inhibit aldosterone-induced increase in plasminogen activator inhibitor-I (PAI-I), the major inhibitor of fibrinolysis and proteolysis, thus reduction in extracellular proteins/collagen accumulation
- Reduce tumor growth factor-β (TGF-β) production
- Increase hepatocyte growth factor, a factor with antifibrotic potential
- Reduce albuminuria. Albuminuria has been shown to stimulate inflammatory response, vasoactive peptide production/release (endothelin), and fibrotic processes.

RASi is recommended for use in

- Individuals with HTN, CKD, and severe albuminuria (G1-G4, A3) without DM
- Individuals with HTN, CKD, DM, and moderate-to-severe albuminuria (G1-G4, A2-A3)

RASi is suggested for use in individuals with HTN, CKD, and moderately increased albuminuria (G1-G4, A2) without DM.

RASi may be considered for use in individuals with albuminuria A1.

Notes regarding the use of RASi in individuals with CKD

- Monitor BP, SCr, and serum potassium within 2 to 4 weeks of initiation or increase in RASi dose, depending on current eGFR and serum potassium.
- Manage hyperkalemia (eg, use potassium binders, low K^+ diet) associated with RASi rather than decreasing or stopping medication.
- Continue RASi unless SCr increases by more than 30% within 4 weeks of drug initiation or dose increase. Investigate for and eliminate causes of SCr increase other than RASi whenever applicable. If there is no other reason for SCr increase, reduce or discontinue RASi.
- Advise contraception in childbearing age women and discontinue RASi during pregnancy planning.
- Avoid any combination of ACEi, ARB, and direct renin inhibitor therapy in individuals with CKD, with or without DM.

Sodium glucose cotransporter-2 inhibitors (SGLT2i)

Mechanisms for the renoprotective effect of SGLT2i

- Afferent vasoconstriction to reduce intraglomerular pressure (proximal tubular sodium chloride wasting causes tubuloglomerular feedback to vasoconstrict afferent arterioles, thereby reducing intraglomerular pressure and glomerular filtration)
- Reduction of renal hypoxia
- BP-lowering effect via sodium wasting

Meta-analysis regarding the use of SGLT2i

- For every 1,000 individuals with CKD and type 2 diabetes mellitus (T2D) treated with SGLT2i for 1 year:
  - 11 fewer CV deaths or hospitalizations for HF

    - Four fewer individuals with AKI, 11 fewer developing CKD progression
    - Approximately one ketoacidosis, approximately one lower limb amputation
- For every 1,000 individuals with CKD without T2D treated with SGLT2i for 1 year:
    - Two fewer CV deaths or hospitalization for HF
    - Five fewer individuals with AKI, 15 fewer developing CKD progression
- Other benefits:
    - Reduce BP, uric acid levels, fluid overload, and risk of serious hyperkalemia
    - Reduce the risk of myocardial infarction (MI)
    - Provide 35% reduction in the risk of CKD progression and 23% reduction in AKI risk
    - Do not increase the risk of hypoglycemia, therefore safe in those without diabetes
- Potential adverse effects:
    - Increased risk for mycotic genital infections in both men and women
    - Increased risk of urinary tract infection (UTI) due to glucosuria
    - Hypovolemia especially if used with diuretics or inadequate oral fluid intake

SGLT2i is recommended for use in individuals with CKD with eGFR greater than 20 mL/min/1.73 m^2 and:

- T2D,
- ACR 200 mg/g Cr or more, or
- HF, irrespective of the level of albuminuria

SGLT2i is suggested for use in individuals with eGFR 20 to 45 mL/min/1.73 m^2 with ACR 200 mg / g Cr or less.

Notes regarding the use of SGLT2i:

- Once initiated, it is reasonable to continue SGLT2i even when eGFR falls below 20 mL/min/1.73 m^2 unless not tolerated or KRT is initiated.
- It is reasonable to hold SGLT2i during prolonged fasting, surgery, or critical medical illness due to concerns for increased risk for (euglycemic) diabetic ketoacidosis (DKA).
- Use with caution in individuals at risk for hypovolemia. Consider lowering dose of diuretics prior to SGLT2i initiation.

Strategies to Reduce CV Risk in CKD (KDIGO 2024)

Statin or statin/ezetimibe combination

- Statin is recommended for secondary prevention in patients with known atherosclerotic cardiovascular disease (ASCVD) (cerebrovascular, coronary, or peripheral vascular disease).
- For primary prevention per KDIGO 2013 general lipid guidelines:
  - Initial assessment of lipid status with a lipid profile is *recommended* for adults with CKD, but follow-up measurements are not required for the majority of patients.
  - In adults aged 50 years or above with eGFR less than 60 mL/min/1.73 m^2 (GFR categories G3a-G5) but not treated with chronic dialysis or transplantation, treatment with a statin or statin/ezetimibe combination is *recommended* (regardless of lipid profile). Large trials have shown safety for use in CKD (including dialysis) of the following: atorvastatin 20 mg, rosuvastatin 10 mg, or simvastatin 20 mg combined with ezetimibe 10 mg daily.
  - In adults aged 50 years or above with CKD and eGFR 60 mL/min/1.73 m^2 or higher (GFR categories G1-G2), treatment with a statin is *recommended*.
  - In adults aged 18 to 49 years with CKD, the use of statin is *suggested* for those with one or more of the following: known coronary artery disease (CAD), DM, ischemic stroke, or

estimated 10-year incidence of coronary death or nonfatal MI more than 7.5% to 10%.

- In adult kidney transplant recipients, treatment with a statin is *suggested*.
- In adults with dialysis-dependent CKD, it is *suggested* that initiation of statins or statin/ezetimibe combination ***not*** *be done*. Statin therapy has been shown to have little or no effect on all-cause mortality or CV outcome in dialysis patients, unlike that observed in the general population. The difference in statin effect is thought to be due to nontraditional mechanisms of disease of CAD in dialysis patients.
- In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, continuation of these agents is *suggested*.

- There is currently no guideline regarding the use of statins for the sole purpose of renoprotection. Data on the renoprotective effects of statins have been mixed.

Type 2 diabetes mellitus

Glycated hemoglobin (Hb) goal

Hemoglobin A1C (HbA1C) goals may range from less than 6.5% to less than 8% in individuals with T2D and CKD. Looser HbA1C goal less than 8% should be used for individuals with advanced CKD (eg, G5), presence of macrovascular complications and multiple comorbidities, short lifespan, poor hypoglycemia awareness, poor resources for management of hypoglycemia, and/or high propensity for treatment that would cause hypoglycemia.

Glucose-lowering strategies

- Maintain healthy and active lifestyle as safely tolerated.
- First-line agents: metformin and SGLT2i. Metformin can be continued safely with very low risk of metabolic acidosis with eGFR 30 mL/min/1.73 m^2 or more. It is suggested that metformin should not be initiated for eGFR 30 to 45 mL/min/1.73 m^2.
- Monitor B_{12} level if metformin use is for more than 4 years.

- Add glucagon-like peptide 1 receptor agonist (GLP-1 RA) if not controlled on metformin and SGLT2i and if possible.
- Others: if all above fail to achieve the goal. See **Appendix A7.11** for other agents.

GLP-1 RAs if not controlled on metformin and SGLT2i

- The use of a long-acting GLP-1 RA is recommended for adults with T2D and CKD who fail to achieve glycemic targets despite the use of metformin and SGLT2i or who cannot tolerate these agents.
- Long-acting GLP-1 RAs are prioritized ahead of insulin in individuals with T2D and CKD. Agents with proven renoprotection and CV benefit and without the need for dose adjustment in CKD include liraglutide, semaglutide (injectable), and dulaglutide.
- Mechanisms for the renoprotective effect of GLP-1 RA:
  - BP-lowering effect
  - Other beneficial effects of GLP-1 RA: weight loss 0.8 to 1.4 kg, improvement in fasting and postprandial lipid profiles, modulation of tissue inflammation or fibrosis
- Caution regarding the use of GLP-1 RA:
  - Hypoglycemic risk of GLP-1 RA is generally low if used alone. However, hypoglycemia risk is increased when used concurrently with insulin or sulfonylureas. Consider dose reduction of these agents when adding GLP-1 RA.
  - Concomitant use of GLP-1 RA and dipeptidyl peptidase 4 inhibitors (DPP-4i) has no added benefit and is not recommended by the U.S. Food and Drug Administration (FDA), American Diabetes Association, and American Clinical Endocrine Association.
  - Consider GLP-1 RA in individuals with T2D, CKD, and obesity for weight loss.

NOTE

Notes regarding DPP-4i (eg, saxagliptin or alogliptin):

Short-term use of a DPP-4i in combination with another oral agent does not appear to increase or decrease the risk of adverse ASCVD outcomes. However, specific DPP-4i (saxagliptin or alogliptin) may increase the risk of hospitalization for HF. The U.S. FDA warns of the risk of hospitalization for HF with DPP-4i, specifically saxagliptin and alogliptin, and recommends discontinuation of these agents in patients who develop HF.

Second-line therapies for reduction of CKD progression, BP control, and CV risk reduction

Mineralocorticoid receptor antagonist (MRA)

Steroidal MRAs (sMRAs) including spironolactone or eplerenone mimic the molecular structure of the natural MR ligands.

- sMRA can decrease proteinuria (albuminuria) and BP when added to RAS inhibition in patients with either diabetic or nondiabetic CKD.
- sMRA may be added with the use of RASi and SGLT2i for the treatment of CKD and T2D.
- sMRA may be used in individuals with HF, hyperaldosteronism, or refractory HTN.
- Adverse effects of sMRAs: hyperkalemia and metabolic acidosis for both agents and reversible decline in GFR; sex hormone–related side effects with spironolactone

Nonsteroidal selective MRA (nsMRA) finerenone was designed to induce a conformational change to the MR complex to reduce its stability and nuclear translocation. Available data reveal a lower level of hyperkalemia with finerenone compared with traditional sMRAs.

- The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD (FIGARO-DKD) placebo-controlled trials and their pooled analysis (FIDELITY) revealed reduced CV risk in individuals with CKD and T2D.
- The use of a nsMRA with proven CV and kidney benefits in individuals with T2D, eGFR 25 mL/min/1.73 m^2 or more,

normokalemia, and albuminuria A1 or higher (30 mg/g Cr) despite being on maximally tolerated RASi is suggested (KDIGO 2024).

- An nsMRA (finerenone) may be added to an SGLT2i in individuals with T2D and CKD (eGFR >25 mL/min/1.73 m^2) with albuminuria greater than 30 mg/g Cr despite being on maximally tolerated dose of ACEi or ARB.
- The effect of combined SGLT2i and finerenone compared with either agent alone is not known and being studied (CONFIDENCE trial).
- Monitor potassium closely with the use of any MRA, whether it be an sMRA or nsMRA.

Lipids: proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) to lower low-density lipoprotein (LDL) in individuals with increased ASCVD risk and not tolerating or controlled with statin/ezetimibe

- PCSK9 is an enzyme produced in the liver. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of the LDL receptors and higher plasma LDL-cholesterol (LDL-C) levels. Blocking PCSK9 with antibodies reduces plasma LDL-C levels.
- Alirocumab and evolocumab are fully humanized monoclonal antibodies that bind free plasma PCSK9.
- Efficacy and Safety of Evolocumab in CKD in the FOURIER Trial revealed benefits extending to patients with CKD stages G2 and G3a to 3b.
- LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across CKD groups.
- Absolute reduction in the composite of CV death, MI, or stroke with evolocumab was numerically greater with more advanced CKD (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.72-0.93 for CKD G2, HR 0.65, 95% CI 0.65-0.95 for CKD stage ≥3).
- The addition of PCSK9i to a maximally tolerated statin-based regimen in individuals at high coronary risk has been shown to

reduce ASCVD risk. Consider prescribing PCSK9i in individuals with CKD and an indication for its use.

Hypertriglyceridemia: icosapent ethyl (Vascepa)

- Icosapent ethyl reduces hepatic very low-density lipoprotein triglyceride (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles.
- May be used as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established CVD or T2D or more additional risk factors for CVD
- May also be used as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

Dietary considerations

- Promote "Mediterranean" diet rich in extra-virgin olive oil high in unsaturated fat: can be associated with CV risk reduction, improved BP, lipid profile, and blood glucose
- Plant-based diets such as fruits, vegetables, nuts, legumes, fish, olive oil, yogurt, and whole grains can ameliorate metabolic acidosis and hyperphosphatemia.

Use of antiplatelet therapy

- Secondary prevention:
  - Low-dose aspirin is recommended for the prevention of recurrent ischemic CVD events (ie, secondary prevention) in individuals with CKD and established ischemic CVD. Benefits outweigh bleeding risk per 2009 meta-analysis by the Anti-thrombotic Treatment Trialists' Collaboration: 1.49%/y lower absolute risk of serious CV events compared with 0.03%/y absolute risk of any major bleeding.
  - Consider $P2Y_{12}$ inhibitor (eg, clopidogrel or ticagrelor) if aspirin intolerant.
  - Consider proton pump inhibitor (PPI) with the use of antiplatelet therapy.

- Primary prevention: Balance of benefits and risks is uncertain. A dedicated large primary prevention aspirin in CKD is ongoing.

Other Factors Attributable to CKD Progression

High-risk *APOL1* gene variants

- The presence of one or more high-risk APOL1 variants (G1/G1, G2/G2, or G1/G2) confers resistance to *Trypanosoma brucei rhodesiense* infection and improves survival in endemic areas. G0 is a low-risk variant.
- Approximately 13% of Black individuals have a high-risk APOL*1* genotype.
- Black individuals with high-risk APOL1 variants have an increased risk for the development of albuminuria, HTN and associated kidney injury, *human immunodeficiency virus* (HIV)-associated nephropathy compared with HIV-positive controls, and focal segmental glomerulosclerosis. In addition, these individuals also develop more rapid CKD progression and increased risk of ESKD, regardless of T2D status.
- Note, however, two-thirds of individuals with two APOL1 risk alleles do not develop ESKD. This observation suggests an interacting role of environmental and/or genetic factors with high-risk APOL1 variants.

Illicit drug use (findings from the Chronic Renal Insufficiency Cohort Study)

- The persistent use of cocaine, heroin, or methamphetamine was associated with increased risk for CKD progression and mortality among adults with CKD.
- The use of marijuana was not associated with CKD progression.

Environmental exposures: Lead and air pollution have been shown to be associated with increased incidence of CKD.

High BMI: Obesity is thought to be associated with ESKD risk when accompanied by metabolic syndrome, diabetes, or HTN.

Proton pump inhibitors

- Observational studies have reported the association of PPI long-term use and incident CKD.
- Cause-effect relationship is not known but theorized to be related to associated hypomagnesemia. Unrecognized PPI-induced tubulointerstitial nephritis may also contribute.

Dietary factors

- Water volume: High intake has not been shown to be renoprotective.
- Sodium: High sodium intake may increase CKD progression risk via exacerbation of existing HTN in salt-sensitive individuals and endothelial damage via oxidative stress and upregulation of TGF-β.
- Coffee intake of 2 cups or more daily may be associated with a lower risk of ESKD in men (without polycystic kidney disease [PKD]).
- Sodas: Sugar-sweetened drinks and diet sodas may be associated with increased CKD risk.

Other suggested factors

- Lipid accumulation in tissues as seen in nonalcoholic fatty liver may be associated with worse outcomes via the release of inflammatory, profibrotic, coagulant, and oxidative mediators.
- Fluid overload has been suggested to be a more important factor than DM for rapid progression and initiation of KRT in CKD stages 4 and 5.
- Hyperuricemia, apolipoprotein E genetic variants, pulse pressure greater than 10 mm Hg, hypomagnesemia

- Of note, hypothyroidism is associated with decreased GFR, but not with an increased rate of CKD progression.

Miscellaneous

Hyperuricemia

- Clinical complications attributed to hyperuricemia include arteriosclerosis, glomerular HTN, glomerulosclerosis, interstitial disease, AKI, metabolic syndrome, nonalcoholic fatty liver disease, HTN, and DM.
- Clinical trials involving uric acid–lowering therapy have not shown clear benefits on CKD progression.

Treatment considerations

- Not recommended: It is not recommended to use uric acid–lowering agents in individuals with CKD and asymptomatic hyperuricemia for the sole purpose of delaying CKD progression.
- Recommended: It is recommended that individuals with CKD and symptomatic hyperuricemia be offered uric acid–lowering intervention.
- Consider: Consider uric acid–lowering therapy for individuals with CKD after a first episode of gout without any known precipitating factor or with serum uric acid levels greater than 9 mg/dL.
- Consider discontinuation of diuretics (if clinically safe) since they can be associated with hyperuricemia.

Notes regarding uric acid–lowering therapies

- Xanthine oxidase inhibitors (eg, allopurinol, febuxostat) are preferred to uricosuric agents (probenecid) in those with CKD and symptomatic hyperuricemia. The Cardiovascular Safety of Febuxostat and Allopurinol in Participants with Gout and Cardiovascular Comorbidities (CARES) double-blind randomized trial of allopurinol versus febuxostat in 6,190 people with gout and prior CVD revealed noninferiority between the two agents with respect to the composite primary CV outcome. However, overall CV mortality was higher in the febuxostat compared with

allopurinol group (HR for death from any cause: 1.22; 95% CI: 1.01-1.47 and HR for CV death: 1.34; 95% CI: 1.03-1.73).

- There is an increased risk of gout flares during the first 3 months following drug initiation in individuals with CKD.
- For the treatment of acute gout in CKD, low-dose colchicine or intra-articular/oral glucocorticoids are preferred to nonsteroidal anti-inflammatory drugs (NSAIDs). Note, however, colchicine is not dialyzable and is contraindicated for CrCl less than 10 mL/min.
- Stevens-Johnson syndrome may occur with allopurinol therapy.
- Both allopurinol and febuxostat can increase urinary xanthine levels, which can be nephrotoxic.
- Of note, in individuals with T2D, post hoc analyses from two large, placebo-controlled RCTs reported that SGLT2i reduced uric acid levels and appeared to reduce gout adverse event reports or initiations of uric acid–lowering therapy.
- Dietary:
  - Avoid alcohol, excessive intake of animal protein, and high-fructose corn syrup.
  - Advise low-fat dairy and high-fiber and plant-based diet.

Endothelin antagonists

- Endothelin 1 mediates the secretion of pro-inflammatory cytokines, growth factors, TGF-β.
  - Type A receptor (ET_AR) mediates vasoconstriction, sodium retention, and podocyte dysfunction.
  - Type B receptor (ET_BR) mediates vasodilation and sodium excretion.
- ET_AR antagonists used in clinical trials involving patients with CKD and albuminuria include avosentan, atrasentan, and zibotentan.
- All agents have been shown to reduce albuminuria. Long-term outcomes and safety data are lacking.

Pentoxifylline (PTF) for albuminuria reduction

- Methylxanthine derivative that acts as a phosphodiesterase inhibitor with anti-inflammatory, antiproliferative, and antifibrotic properties
- 2017 meta-analysis involving 11 RCTs (*n* = 705) on the efficacy and safety of PTF (400-1,200 mg/d) plus ACEi/ARB in patients with CKD stages 3 to 5 revealed a reduction in urine albumin excretion from 900 to 791 mg/d and alleviation in eGFR decline.
- A small RCT (de Morales et al, 2019) revealed that long-term treatment with PTF may slow the rate of progression of CKD and reduce CV risk.

Nonrenal biomarkers in CKD

Troponin

- Increased troponin level is associated with a 2- to 4-fold increased risk of all-cause mortality and major CV events.
- In patients with asymptomatic CKD, elevated troponin levels may indicate chronic structural heart disease (eg, left ventricular hypertrophy [LVH], diastolic dysfunction, reduced ejection fraction) rather than acute coronary syndrome.

Brain natriuretic peptide (BNP)

- BNP is a less reliable marker of volume overload in patients with CKD. Interpret with caution in patients with eGFR less than 60 mL/min/1.73 m^2.
- However, BNP levels provide a good index for LV mass and dysfunction.

D-Dimer level can be elevated in CKD. A higher cutoff value may be needed in patients with advanced CKD to rule out pulmonary embolism.

Acute phase reactants associated with CV risk that may be elevated in CKD include fibrinogen and ceruloplasmin.

MANAGING CKD COMPLICATIONS

Metabolic Acidosis (Total CO_2 <22 mEq/L)

Prevalence: 7%, 13%, and 37% of patients with CKD stages 2, 3, and 4, respectively

Factors contributing to metabolic acidosis

- Decreased total urinary ammonium (NH_4^+) excretion: Lower urinary NH_4^+ excretion/higher H^+ retention is associated with increased CKD progression risk and ESKD, even in the absence of overt clinical metabolic acidosis. Early identification of H^+ retention may be beneficial. Reduced urinary citrate level is being studied as a surrogate for H^+ retention.
- Reduced bicarbonate generation in proximal and distal tubules
- Use of acid-containing medications (eg, metformin HCl, gabapentin HCl, sevelamer HCl)

Adverse clinical effects associated with metabolic acidosis

- Increased protein degradation, catabolic rate, muscle wasting
- Impaired vitamin D synthesis, bone metabolism, loss of bone density
- Accelerated CKD progression (due to activation of profibrotic and pro-inflammatory pathways and worsening of proteinuria and tubulointerstitial injury mediated by Ang II, endothelin 1, aldosterone, and intrarenal ammonia)
- Altered endocrine functions: decreased insulin sensitivity, decreased insulin-like growth factor 1 (IGF-1) levels and responsiveness of IGF-1 to growth hormone administration, and reduced thyroid function (reduced T3 and T4 with normal thyroid-stimulating hormone and blunted response to thyrotropin)
- Increased all-cause mortality in CKD, ESKD, and renal transplant recipients
- Others: increased oxidation of branched-chain amino acids (valine, leucine, isoleucine); decreased albumin synthesis

Correction of CKD-related metabolic acidosis

- KDIGO 2012 goal to keep serum HCO_3^- in the range of 22 to 29 mEq/L (but not exceeding the upper limit of normal) is being questioned due to the lack of any modifying effect on kidney outcome from 2020 systematic review. Goal serum HCO_3^- 16 mEq/L or higher to avoid severe metabolic acidosis is being considered awaiting updated KDIGO guidelines.
- Alkalinization strategies:
  - Increase consumption of base-producing fruits and vegetables, plant-based proteins.
  - Decrease animal-based protein intake.
  - Alkalinization with $NaHCO_3$ appears to be safe without increasing fluid retention or HTN risk.
  - Veverimer, an oral nonabsorbed gut HCl binder, is being evaluated as a novel therapy for metabolic acidosis in CKD. Its use is associated with increased serum [HCO_3^-] and improved physical function. Further studies are ongoing.

CV Complications

Hypertension

- Prevalence of HTN reaches approximately 80% to 90% in patients with CKD stage G3 or above.
- Pathogenesis: sodium retention, increased peripheral resistance due to increased activities of the sympathetic and renin-angiotensin aldosterone systems (RAAS)

Management of high BP in patients with CKD (KDIGO 2024) (also see **Chapter 5: Hypertension**)

- Targeting standardized office SBP to less than 120 mm Hg, if safely tolerated, is suggested in adults with CKD.
- ACEi or ARB is recommended for:
  - Individuals with high BP, CKD, and severe albuminuria (G1-G4, A3) without DM

    - Individuals with high BP, CKD, and moderate-to-severe albuminuria (G1-G4, A2 and A3) with DM
- ACEi or ARB is suggested for individuals with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without DM.
- It is recommended to avoid combination use of ACEi, ARB, and direct renin inhibitor therapy in patients with CKD, with or without DM.
- The use of a dihydropyridine calcium channel blocker or an ARB as the first-line antihypertensive agent in adult kidney transplant recipients is recommended.

Fluid overload

- Impaired pressure natriuresis
- Increased renal sodium reabsorption due to increased Ang II and aldosterone
- Sodium restriction, diuretics as needed

Hyperlipidemia

Recommendations for statin use in CKD and ESKD are discussed previously.

Sudden cardiac deaths

- Account for up to 35% of all deaths in prevalent dialysis patients in the United States. This is 20 times higher than that observed in the general population.
- Potential contributing factors: low levels of long-chain n-3 fatty acids, low dialysate concentrations of potassium (<2 mEq/L) and calcium (<2.5 mEq/L), inadequate dialysis, higher ultrafiltration (UF) volumes (>10 mL/h/kg body weight), long interdialytic window (higher risk on Sundays for patients receiving HD on Monday/Wednesday/Friday and Mondays for patients receiving HD on Tuesday/Thursday/Saturday)

- Placement of an implantable cardioverter-defibrillator (ICD) for primary prevention is indicated in dialysis patients with LV ejection fractions 35% or less.

Atrial fibrillation (AF)

- A stepwise increase in incident AF is observed among patients with higher CKD stages and increasing ACR. AF prevalence ranges from 16% to 21% in patients with nondialysis CKD and 15% to 40% in those on dialysis.
- There is also a progressively increased risk of both ischemic stroke and hemorrhage among patients with AF and more advanced CKD.

Rhythm control: Indications for rhythm control strategy in patients with CKD mirror those in the general population.

Rate control: Pharmacokinetics and dialyzability of rate control agents should be considered.

Anticoagulation in CKD G4 to G5

- Oral anticoagulation should be considered for stroke prevention in individuals with CKD and AF with or without increased CHA2DS2-VASc score. Patients with CKD are at high risk even with a score of 0 or 1. A bleeding risk score (HAS-BLED) should also be reviewed and modified as needed (eg, use of PPI, minimizing alcohol consumption). Risks and benefits must be reviewed with patients.
- The use of non–vitamin K antagonist direct oral anticoagulants (DOAC) is recommended over the use of vitamin K antagonists (warfarin) for thromboprophylaxis in individuals with CKD G1 to G4 with AF due to their improved efficacy and relatively similar safety profile. Warfarin use can be associated with higher risk of vascular calcification and calciphylaxis.
- DOAC dose adjustment per GFR is required. The U.S. FDA has approved reduced doses of apixaban, edoxaban, and rivaroxaban in patients with eGFR 15 to 30 mL/min/1.73 m^2. Low-dose dabigatran 75 mg bid has also been approved for these patients.

- Discontinuation of DOAC prior to elective procedures must be considered. Duration of preprocedural discontinuation is based on specific DOAC, bleeding risk of the procedure, and GFR and ranges from 24 hours or more to 96 hours or more.

Anticoagulation in CKD G5D

- Specific recommendations are still lacking. Some experts would anticoagulate higher risk individuals based on CHA2DS2-VASc scores.
- Anticoagulation is suggested to be "individualized" and discussed with patients based on risks and benefits. Other options including left atrial appendage occlusion or "no therapy" may be considered based on multidisciplinary team discussion.

Atrial flutter

In patients with CKD and atrial flutter, radiofrequency ablation is considered first-line therapy due to its high success and low complication rates.

Coronary artery disease (CAD)

Epidemiology

- Patients with CKD stages G3a to G4 have double and triple CV mortality risk, respectively, relative to patients without CKD.
- Probability of developing CAD increases linearly with GFR below 60 to 75 mL/min/1.73 m^2.

CAD risks

- Nontraditional risks (serum phosphate, albumin, C-reactive protein, dialysis vintage) may predict major CV events in HD patients.
- Traditional risks (hyperlipidemia, BP, pulse pressure) may not predict outcomes.

Clinical manifestations

- Atypical, "oligosymptomatic" presentation is common: Chest, arm, shoulder, or neck pain is only reported in 44% among patients

with acute myocardial infarction (AMI) and CKD stages G3a or above versus 72% among those with preserved kidney function. Anginal equivalents such as dyspnea and fatigue may be more common and must be recognized.

- Patients with CKD may more commonly present with AMI rather than stable exertional angina.
- Presentation is more likely to be non–ST-elevation AMI (non-STEMI) rather than STEMI.

Routine management of CV risks per KDIGO

- Patients with CKD are less likely than non-CKD counterparts to receive CV intervention, CV diagnostic studies, and treatment including aspirin and β-blockers. Level of care for ischemic heart disease (IHD) should not be "prejudiced" by their CKD.
- Adults at risk for atherosclerotic disease should be offered antiplatelet therapy if the benefit outweighs bleeding risk.
- In patients with eGFR less than 60 mL/min/1.73 m^2, BNP/N-terminal-proBNP and troponin levels should be interpreted with caution.
- Invasive interventions: Coronary artery bypass grafting has been shown to be associated with a lower risk of death compared with percutaneous coronary intervention at 5-year follow-up for multivessel disease (USRDS data 1997-2009).
- The use of drug-eluting stent improves revascularization of blood vessels compared with a bare-metal stent in patients with CKD stage 3.
- Addition of spironolactone to ACEi or ARB therapy in patients receiving KRT: If safely tolerated (ie, hyperkalemia), may reduce LVH and improve survival.

Other interventions

- Fish oil (eg, 4 g daily) has been suggested to lower the risk for CV events.
- Smoking cessation

Invasive versus intensive medical therapy for CAD

- In stable stress test confirmed IHD, an initial conservative approach using intensive medical therapy is suggested to be an appropriate alternative to an initial invasive strategy.
- Initial intensive strategy may still be preferred for those with CKD with acute or unstable CAD, patient-perceived unacceptable level of angina, ischemia-associated LV systolic dysfunction (eg, ejection fraction ≤35%), or left main disease.

Anemia Associated With CKD

Anemia associated with CKD is a hypoproliferative normochromic normocytic anemia.

Onset

- Typically occurs at CKD G3a for males and G3b for females
- Patients with DM and chronic tubulointerstitial (CTI) disease tend to have anemia at earlier CKD stage; anemia may be more severe with CTI disease.
- Patients with PKD tend to have anemia at later stage and less severe anemia.

Complications of anemia

- Fatigue, poor quality of life, difficulty with concentration, impaired judgment, sleep disturbance
- LVH, coronary heart disease
- Sexual dysfunction
- Impaired immune response
- Platelet dysfunction
- Anemia is a "risk multiplier" for mortality in patients with CKD.
- Possible risk factor for progression of CKD

Pathogenesis of anemia in CKD

- Reduced renal erythropoietin (EPO) production due to loss of kidney mass. EPO is synthesized by peritubular interstitial fibroblasts and regulated as follows:

- Under normoxic conditions, the hypoxia-inducible factor-α (HIF-α) is hydroxylated by prolyl hydroxylase domain (PHD) enzymes, followed by "ubiquitination" by von Hippel-Lindau protein (pVHL) for subsequent degradation by proteasomes. "Ubiquitination" is a process whereby a protein is "marked for degradation."
- Under hypoxic conditions, HIF-α is not hydroxylated because of decreased PHD activity. The nonhydroxylated HIF-α translocates into the nucleus where it dimerizes with HIF-β, followed by binding of the HIF-α-HIF-β dimer to the hypoxia response element (HRE) at regulatory regions of target genes, thereby activating the transcription of hypoxia-related genes including EPO (**Figure 4.1**).

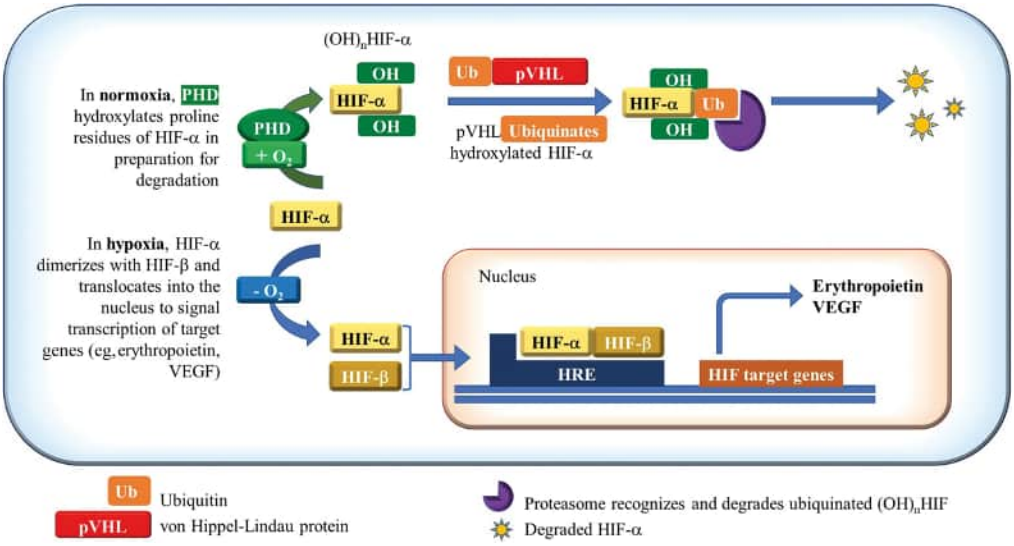

FIGURE 4.1 Regulation of hypoxia-inducible factor (HIF) by prolyl hydroxylase domain enzymes. HIF-α is continuously made in cells. In normoxic condition, PHD hydroxylates HIF-α at specific proline residues. The hydroxylated HIF-α is tagged for proteasomal degradation by pVHL, a process called ubiquitination. Under hypoxic condition, PHD leaves HIF-α unhydroxylated, allowing it to form dimers with HIF-β and translocate into the nuclei. Binding of the HIF-α-HIF-β dimers to the hypoxia response element (HRE) activates the transcription of HIF target genes, including erythropoietin and vascular endothelial growth factor (VEGF), among others.

Abbreviations: $(OH)_nHIF-\alpha$, hydroxylated HIF-α; PHD, prolyl hydroxylase domain enzyme; pVHL, von Hippel-Lindau protein; Ub, ubiquitin; .

- Anemia of CKD occurs in part because of:
  - Insufficient HIF expression and function, as well as
  - Transformation of EPO-producing fibroblasts into EPO-nonproducing myofibroblasts
- Inflammatory state in CKD reduces EPO production and increases hepatic synthesis of hepcidin. Hepcidin reduces gastrointestinal (GI) absorption of iron and enhances iron sequestration in macrophages, hepatocytes, and duodenal enterocytes. HIF can also suppress hepcidin.
- Ferroportin is a transmembrane protein on macrophages and enterocytes that normally exports intracellular iron into circulation for erythropoiesis. Hepcidin binds to and internalizes ferroportin, thereby reducing iron export into circulation by macrophages, hepatocytes, and duodenal enterocytes into circulation for erythoipoiesis.
- RBC half-life is shortened in uremia.
- Severe secondary hyperparathyroidism (hPTH) can induce bone marrow fibrosis and results in ineffective erythropoiesis.
- Contributing factors to anemia following kidney transplant: iron deficiency, inflammatory state, infection, drug induced (mycophenolate, azathioprine, ACEi, ARB, trimethoprim-sulfamethoxazole, ganciclovir)

Treatment of anemia of CKD (KDIGO suggestions)

- Monitor Hb at least yearly for patients with CKD G3, twice yearly for stage G4, every 3 months for stage 5.
- Anemia evaluation: peripheral blood smear, haptoglobin, lactate dehydrogenase, C-reactive protein, B_{12}, folate, liver function, paraproteinemia (eg, M-protein, free light chains, urine Bence-Jones), thyroid-stimulating hormone, stool analysis
- Refer to gastroenterologists, gynecologists, and urologists as clinically indicated to investigate the source of blood loss in patients with ferritin less than 45 mg/L.

- EPO level is not generally checked because "normal" level may still be inadequate for patients with CKD due to possible bone marrow resistance to EPO.
- Exclude common causes of anemia.

Correction of iron deficiency

- Definition of iron deficiency:
  - Systemic iron deficiency (reduced ferritin [reflecting iron storage] and reduced transferritin saturation [TSAT; reflecting iron availability in circulation]): ferritin less than 100 mg/L for CKD G1-G5 or less than 200 mg/L for CKD G5HD; TSAT is less than 20%.
  - Iron-restricted erythropoiesis (high ferritin and reduced TSAT): ferritin of greater than 100 to 200 mg/L; TSAT is less than 20%.
  - For the combination of low TSAT and high ferritin greater than 500 ng/mL: Evaluate for any inflammatory or infectious condition and malnutrition.
- Suggestions for iron supplementation:
  - CKD 5HD: ferritin of 500 ng/mL or less and TSAT of 30% or less
  - CKD not receiving dialysis or treated with PD: ferritin of less than 100 ng/mL and TSAT of less than 40%, or ferritin of 100 ng/mL or more and less than 300 ng/mL, and TSAT is less than 25%.
  - It is reasonable to withhold iron therapy if ferritin is 700 ng/mL or more or TSAT is 40% or more.
- Adverse effects associated with intravenous (IV) iron include increased oxidative stress, endothelial injury, vascular calcifications and plaque formation, and impaired leukocyte function, which may facilitate bacterial growth.
  - The use of IV iron in patients with systemic infections is not recommended.

- Hold IV iron if ferritin is greater than 500 ng/mL. Note, however, that even when KDOQI iron parameters have been reached, anemia may still respond to iron therapy in some patients. This is referred to as "functional iron deficiency." Clinical judgment is required.
- Monitor iron status (TSAT and ferritin) 3 months or more during therapy with erythropoiesis-stimulating agent (ESA).

Use of ESA

- Avoid use in patients with active malignancy particularly when cure is anticipated or history of stroke (increased thromboembolic risk and survival in some cancers).
- Initiate when Hb values trend downward to levels less than 9 to 10 g/dL after iron store has been repleted. Monitor Hb 1 month or more while on ESA.
- ESA is not recommended to achieve Hb greater than 11.5 g/dL due to the potential increased risk for CV events.
- Monitor Hb every 3 months when on stable ESA doses.
- Empirical use of adjuvant therapies including androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and PTF is not suggested.
- Carnitine is involved in RBC plasma membrane remodeling, hence RBC survival. A 2021 meta-analysis involving 18 trials and 1,090 participants revealed carnitine supplements improved response to ESA and decreased ESA doses in patients receiving HD.
- Potential adverse effects of ESA: major CV events, malignancy, dialysis access thrombosis, and HTN

ESA hyporesponsiveness

- Initial ESA hyporesponsiveness is defined as having no increase in Hb levels from baseline after 1 month of appropriate ESA weight-based dosing.
- ESA dose escalation greater than doubling of initial weight-based dose should be avoided.

Initial ESA hyporesponsiveness despite appropriate weight-based dosing:

- Evaluate for common deficiencies: iron, vitamin B_{12}/folate/carnitine
- Other possible causes: inflammatory or infectious state, underdialysis, severe secondary hPTH, aluminum toxicity, use of RAS inhibitors, underlying bone marrow disorders (BMDs), hemoglobinopathies, blood loss/hemolysis, immunosuppressive medications
- Bone marrow biopsy may be necessary to determine the cause of ESA hyporesponsiveness.

Subsequent ESA hyporesponsiveness

- This is defined as having two increases in ESA doses up to 50% beyond the initial stable maintenance dose for the desired Hb.
- Evaluation for subsequent hyporesponsiveness:
  - Routine evaluation similar to initial hyporesponsiveness above
  - Consider pure red cell aplasia: antibody-mediated destruction of ESA that may occur in patients on ESA for greater than 8 weeks. Very rare
  - Suspect pure red cell aplasia if there is a sudden and rapid drop of Hb, normal white blood cell (WBC) and platelet count, and low reticulocyte count

HIF stabilizers: prolyl hydroxylase inhibitors of HIF (HIF-PHIs)

- Current FDA-approved HIF-PHIs in the US include daprodustat and vadadustat.
- The use of ESA is suggested as first-line therapy rather than HIF-PHIs in individuals with anemia of CKD. Conversion from ESA to HIF-PHIs may be considered in those who do not respond to ESA. Do not use ESA and HIF-PHIs concurrently.
- Potential advantages of HIF-PHIs:
  - Provide more physiologic level of endogenous EPO

    - Potential increased availability of iron for erythropoiesis (Recall HIF suppresses hepcidin. Lower level of hepcidin with the use of HIF-PHIs is beneficial because hepcidin reduces GI absorption of iron and enhances iron sequestration in macrophages, hepatocytes, and duodenal enterocytes.)
    - Oral administration
- Potential concerns for HIF-PHIs:
    - Angiogenesis and tumor-producing effects
        - HIF signaling activates VEGF (vascular endothelial growth factor) transcription, thus allowing angiogenesis to support rapidly growing tumors (or proliferative diabetic retinopathy).
        - HIF may promote tumor metastasis via stimulation of epithelial-to-mesenchymal transition, thereby inducing tumor cell invasion.
        - Potential risks for adverse events with HIF-PHIs: prior CVE (cerebrovascular events; eg, stroke, myocardial infarction), thromboembolic events, vascular access thrombosis, hepatic impairment, seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat)
- Nonerythropoietic effects of HIF-PHIs may adversely affect disease development or progression in those with active cancer or cancer in complete remission in less than 2 to 5 years, polycystic kidney disease, proliferative retinopathy, or pulmonary arterial hypertension. The use of HIF-PHIs is contraindicated in pregnancy.

Notes about the FDA-approved HIF-PHIs in the US

- In the United States, both daprodustat and vadadustat are only approved for the treatment of anemia of CKD in patients who have been receiving HD for at least 4 and 3 months, respectively. All other HIF-PHIs are not available in the United States.
- The use of HIF-PHIs is contraindicated in patients with uncontrolled HTN. Additionally, with daprodustat, concurrent use

of strong CYP2C8 inhibitors (eg, gemfibrozil) is contraindicated. Monitor thyroid function with the use of vadadustat.

- U.S. box warning for both daprodustat and vadadustat: "Increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access". It is reasonable to suspend HIF-PHIs (or ESA) in acute stroke, vascular access thrombosis, or thromoembolic events.

RBC transfusions

- Avoid if possible due to multiple potential complications, including rare transmission of infections, iron overload, volume overload, hyperkalemia from prolonged shelf-life, and allosensitization in future transplant candidates.
- The decision to transfuse should be based on signs and symptoms of anemia rather than any hemoglobin threshold.

CKD-Mineral Bone Disease (CKD-MBD)

CKD-MBD refers to disorders of systemic mineral metabolism involving abnormalities in biochemical profile, bone turnover, mineralization and volume, and/or vascular and soft tissue calcifications. Biochemical profile refers to serum calcium, phosphate, bone-specific alkaline phosphatase (BAP), and parathyroid hormone (PTH). KDIGO 2017 recommendations on monitoring and management of CKD-MBD are summarized in **Table 4.3**. See **Chapter 3: Calcium, Phosphorus, Magnesium, Stones** for the pathogenesis and management of secondary hPTH.

Table 4.3 Summary of Kidney Dialysis Initiatives on Global Outcomes (KDIGO) CKD-MBD recommendations

	CKD stage	3	4	5/5D
Biochemical profile	Ca, PO_4	q6-12m	q3-6m	q1-3m
		• May increase monitoring frequency for trends, treatment efficacy, and side effects		

	CKD stage	3	4	5/5D
		• Therapeutic decisions should be based on trends rather than a single value. • *Individual* values of Ca and PO_4 should be evaluated together to guide management rather than the Ca × PO_4 *product*.		
	Intact PTH (iPTH)	Based on baseline level and CKD progression	q6-12m	q3-6m
	Bone specific AP	q12m or more frequently in the presence of elevated iPTH		
	25(OH)D	• Monitoring frequency depends on baseline values and therapeutic intervention. • Vitamin D deficiency and insufficiency may be corrected as for the general population.		
Diagnosis	Bone	• In patients with CKD-MBD and/or risk factors for osteoporosis, BMD testing is suggested if results will impact treatment decisions. • Performing a bone biopsy is reasonable if result impacts treatment decision. • Measurements of iPTH and AP can be used to evaluate bone disease.		
	Vascular calcifications	• A lateral abdominal radiograph and an echocardiogram may be used to detect vascular calcifications/valvular calcifications, respectively, in lieu of CT-based imaging.		
Treatment	Serum phosphate	• Treatment of CKD-MBD should be based on serial Ca, PO_4, and iPTH assessments. • Treat progressively/persistently elevated PO_4 levels, eg, dietary PO_4 restriction ± use of phosphate binders. Lower PO_4 toward normal range. • Restrict dose of calcium-based phosphate binders.		

	CKD stage	3	4	5/5D

		• Avoid aluminum-containing phosphate binders.
		• For patients receiving hemodialysis:
		  • Use dialysate Ca^{2+} concentration of 1.25 to 1.50 mmol/L (2.5-3.0 mEq/L).
		  • Increase dialytic phosphate removal if persistent hyperphosphatemia.		

	Intact PTH	• Optimal iPTH level is not known. • For patients with CKD G5D: Maintain iPTH levels ~2-9 times upper normal limit. • For elevated levels, evaluate modifiable factors (Ca^{2+}, PO_4, 25-vitamin D levels). • Calcitriol and vitamin D analog should not be used routinely but reasonable to be used for CKD G4-G5 and severe and progressive hyperparathyroidism. • Calcimimetics may be used for PTH-lowering therapy ± calcitriol or vitamin D analogs. • In children, calcitriol and vitamin D analogs may be considered to maintain age-appropriate serum Ca^{2+} levels.		
	Use of bisphosphonates, osteoporosis medications, h-GH	• In patients with biochemical abnormalities, low BMD, and/or fragility fractures, treatment choices should reflect the magnitude and reversibility of the biochemical abnormalities and CKD progression. Consider bone biopsy. • In children/adolescents CKD G2-G5D and related height deficits, use recombinant h-GH after addressing malnutrition and biochemical abnormalities of CKD-MBD.		

Abbreviations: AP, alkaline phosphatase (bone specific); BMD, bone mineral density; Ca, calcium; CKD, chronic kidney disease; CT, computed tomography; h-GH, human growth hormone; iPTH, intact parathyroid hormone; MBD, mineral bone disease; PO_4, phosphate.

CKD-related bone diseases are summarized in **Table 4.4**.

CKD-MBD bone disease

Table 4.4

Bone disease	Key bone morphology	Comments
Osteitis fibrosa cystica	• High bone turnover • Normal or defective mineralization	• Seen with 2° hPTH • Most common bone disorder seen in HD patients
Adynamic bone disease	• Low bone turnover • Low mineralization	• Most common bone disorder seen in PD patients • Risks: oversuppression of 2° hPTH with VDRA and calcium-based phosphate binders, DM, advanced age, aluminum deposition
Osteomalacia	• Low bone density and low mineralization	• Low bone formation and bone density • May be seen with aluminum toxicity
Mixed uremic osteodystrophy	• Mix between osteitis fibrosa cystica and osteomalacia (OM) • High bone turnover (OFC) • Abnormal mineralization (OM)	• Most common bone disorder in patients with CKD G3-G5
Osteoporosis	• Increased bone breakdown relative to bone production • Abnormal mineralization	• Treatment of concurrent CKD-MBD takes precedence over osteoporosis in patients with CKD. • Obtain alkaline phosphatase in addition to DEXA scan to determine low, normal, vs high bone turnover to guide treatment (see text).

Abbreviations: 2° hPTH, secondary hyperparathyroidism; CKD, chronic kidney disease; DEXA, dual-energy x-ray absorptiometry; DM, diabetes mellitus; HD, hemodialysis; MBD, mineral bone disease; PD, peritoneal dialysis; PTH, parathyroid hormone; VDRA, vitamin D receptor agonist.

Bone "TMV" terminology

- **T**urnover (reflects osteoblastic and osteoclastic activity): low, normal, or high
- **M**ineralization: normal or abnormal
- **V**olume (reflects net bone formation and resorption rates and is related to bone porosity, strength, and fragility): low, normal, or high
- Renal osteodystrophy refers to various bone histomorphologic abnormalities due to disturbances in bone turnover, mineralization, and volume as a consequence of CKD-MBD. Classifications of the types of renal osteodystrophy can be based on abnormalities of bone turnover and mineralization. All bone disorders are associated with increased fracture risks.

Bone biopsy

- Gold standard to diagnose bone disorders
- Bone biopsy is obtained from anterior iliac crest after tetracycline labeling at two different times separated by 11 to 14 days. Tetracycline binds to newly formed bone at unmineralized bone interface. Measuring the distance between the two lines allows for calculation of bone formation rate during that interval.

Indications for bone biopsy

- Persistent incapacitating bone pain
- Recurrent fragility fractures
- Unexplained hypophosphatemia
- Concerns for aluminum (Al) toxicity (rare; seen in the past with Al-based phosphate binders)
- Prior to initiating therapy with bisphosphonates for osteoporosis to exclude mineralization defects and to assess bone turnover
- Prior to parathyroidectomy to rule out osteomalacia (OM) and to ensure high PTH level is associated with high bone turnover, not low bone turnover. This is particularly important in kidney

transplant recipients where hypercalcemic hPTH may be associated with normal or low bone turnover.

- Young individuals with rapid progression of vascular calcifications

Osteitis fibrosa cystica (OFC)

- High bone turnover disease: high rates of bone formation and resorption
- Most common bone disorder observed in patients receiving HD

Bone histomorphology: increased osteoblastic and osteoclastic activity with a high fraction of trabecular surface covered by osteoid seams, osteoid-osteoblast interface, abnormal collagen deposition, marrow fibrosis (high **T**urnover, normal or reduced **M**ineralization to the marked increase in bone turnover)
Risk for OFC: condition seen with high PTH levels
Laboratory findings: high BAP

Adynamic bone disease (ABD)

- Low rates of bone formation and resorption, may be evidenced by low tetracycline uptake
- Most common bone disorder observed in patients receiving PD
- May be associated with ectopic calcification (increased systemic calcification in the setting of poor bone uptake of calcium)

Bone histomorphology
Low **T**urnover with inactive-appearing osteoblasts, reduced osteoclastic activity, thin osteoid seams, low **M**ineralization; Bone **V**olume is low to normal
Risks for ABD

- Oversuppression of PTH with calcitriol, calcimimetics, chronic exposure to high calcium (eg, calcium-containing phosphate binders, high calcium dialysate)
- Resistance to PTH, parathyroidectomy
- Advanced age
- DM

- Aluminum deposition (aluminum-based phosphate binders used in the past)

Laboratory findings for ABD

- High BAP suggests high turnover bone disease, thus rules out ABD.
- Relatively low/normal serum intact PTH level
- Hypercalcemia (serum calcium is not taken up by bone due to low bone formation)
- Relatively normal to low serum phosphorus (due to low bone resorption)

Osteomalacia (OM)

OM is characterized by reduced mineralization with prolonged mineralization lag time.

Bone histomorphology: Low bone density, poor bone **M**ineralization; bone **T**urnover is variable.

Risks for OM: use of aluminum-based phosphate binders, vitamin D deficiency, hypocalcemia, hypophosphatemia, metabolic acidosis, exposure to heavy metals

Mixed uremic osteodystrophy (MUO)

- Bone disorder with combined features of OFC and OM
- Most common bone disorder in patients with CKD stages 3 to 5

Bone histomorphology: characterized by high bone **T**urnover (seen with OFC) and abnormal **M**ineralization with prolonged mineralization lag time (seen with OM)

Risks for MUO: elevated PTH levels and factors leading to impaired bone mineralization, for example, vitamin D deficiency, hypocalcemia, hypophosphatemia, metabolic acidosis, and exposure to heavy metals

Osteoporosis

- Increased bone breakdown relative to bone production

- Bone density (or mass) is at least 2.5 standard deviation less than peak bone mass.

Diagnosis: dual-energy x-ray absorptiometry (DEXA) scan every 1 to 2 years (see Diagnostic Testing below)

Management of osteoporosis in patients with CKD

- Treatment of concurrent CKD-MBD has priority over treatment of osteoporosis.
- If T-score is −2.5 or less, assess bone turnover with BAP.
  - If BAP is elevated, high bone turnover is likely, initiate antiresorptive agent (eg, bisphosphonates, denosumab).
  - If BAP is low, low bone turnover is likely, initiate anabolic agent (eg, teriparatide, abaloparatide).
  - If BAP is within the middle of normal range, perform bone biopsy to exclude low bone turnover disease prior to administration of bisphosphonates.
    - Severe hypocalcemia may occur with bisphosphonates in patients with vitamin D deficiency.
    - Safety issue: FDA warnings against the use of bisphosphonates in patients with GFR less than 30 mL/min/1.73 m^2
    - KDIGO suggests *not* to prescribe bisphosphonate to patients with eGFR less than 30 mL/min/1.73 m^2 without a strong clinical rationale.
- Strict phosphorus/protein restriction improves renal osteodystrophy but thought to worsen osteoporosis. Low-protein intake is associated with lower BMD.
- Other therapeutic options:
  - Assess adequacy of protein intake and correct metabolic acidosis
  - Maintain muscle mass to increase workload for stimulation of bone turnover
  - Romosuzomab, an antisclerostin antibody, may be used in postmenopausal osteoporosis with high fracture risk. Potential

increased cardiovascular complication risks and hypocalcemia must be considered.

Drugs associated with increased osteopenic fracture risks: PPIs, antidepressants, anticoagulants, loop diuretics
Drugs that may increase bone density and reduce fracture risks: thiazide diuretics
Drugs with inconsistent data regarding beneficial effects on bone density and fracture risks: statins, nitrates, β-blockers

Osteopenia

- Similar to osteoporosis but milder condition
- Bone density is 1 to 2.5 standard deviation less than peak bone mass.
- Diagnostic testing:
  - DEXA determines both mineral content and bone area.
    - Limitations: DEXA may overestimate BMD in patients with CKD, likely due to vascular calcifications and/or hPTH-induced increased trabecular-to-cortical bone ratio.
    - KDIGO suggests DEXA testing to assess fracture risk in patients with CKD G3a to G5D "if the results will impact treatment decisions."
  - Quantitative computed tomography (CT) measures three-dimensional (3D) bone volume and can differentiate cortical and trabecular bone geometry and morphology.
  - Micro-magnetic resonance imaging (MRI): high-resolution MRI
  - Quantitative ultrasound: measures appendicular skeletal density (most often calcaneal bone), may be better than DEXA. Limited data in CKD

Extraosseous and Vascular Calcifications

Basic arterial layers starting from outside to lumen: adventitia > media > intima
Medial artery calcifications (MACs)

- Concentric calcifications can lead to arterial stiffening.
- MAC is associated with better survival compared with those with intimal calcifications (seen with classic CAD risks), but worse survival compared to those with no calcification.
- The use of denosumab has been suggested to be beneficial in reversing/treating vascular calcifications.
  - In a nonrandomized study involving 21 patients with secondary hPTH, denosumab was shown to be protective against coronary artery calcification and beneficial to increasing bone density.
  - In an observational study during 2009 to 2020 involving 58 patients with an 8-year vintage of dialysis at one center, long-term use (30 months) of denosumab was effective in reversing/treating aortic arch calcifications in patients undergoing HD.
  - A 6-month pilot study enrolling patients with secondary hPTH and low bone mass (T-score <-2.5) owing to dialysis showed that denosumab suppressed the progression of coronary artery calcification and regressed osseous calcification in severe cases of high bone turnover.
  - More data are needed.

Immune Dysfunction

Contributing factors

- Diabetes, malnutrition, peripheral vascular disease, skin breaks (eg, dialysis access, diabetic foot ulcers)
- Impaired host defense mechanisms affecting all cell lines (neutrophils, monocytes, lymphocytes, dendritic cells, macrophages)

Clinical impact

Increased infection risks

- Increased infection risks for *Staphylococcus* sp., *Pseudomonas* sp., other gram-negative bacteria, atypical bacteria including *Mycobacterium tuberculosis*, viruses (herpes simplex)
- Patients with ESKD are estimated to have a 50-fold increased risk in developing active TB infection.
- Interferon release assays (eg, QuantiFERON or T-SPOT.TB testing), which measure the response of sensitized T cells to mycobacterial antigens, correlate with past TB radiologic evidence better than traditional skin testing

Increased malignancy risks

- Increased malignancy risk has been reported in patients receiving KRT involving kidney, bladder, cervix, multiple myeloma, thyroid, and other endocrine glands.
- No increased risks reported in breast, prostate, stomach, intestine, or lungs.

Management: The malignancy screening guidelines for CKD are not well established. At minimum, screen per routine for age, gender, personal risks, family history, and pretransplant evaluation.

Acquired Cystic Kidney Disease (ACKD) and Renal Cell Carcinoma (RCC)

Definition: Presence of more than three to five macroscopic cysts in individuals with CKD with normal or small kidneys without a hereditary cause of cystic disease

Prevalence

- Prevalence increases with CKD vintage and may occur prior to dialysis
- Prevalence at dialysis initiation has been estimated to be approximately 5% to 20% but can increase up to 80% to 100% by 10 years on dialysis.

Pathogenesis of ACKD is likely multifactorial and may be related to:

- Loss of nephrons followed by tubular cell hypertrophy, hyperplasia, and epithelial cyst formation.
- Activation of proto-oncogenes and accumulation of mutagens in a uremic milieu
- Genetic susceptibility

Malignant transformation to RCC

- Cumulative incidence less than 1% up to 7% among ACKD
- Up to 40-fold increased risk of RCC in ACKD compared with the general population
- Risk factors associated with RCC transformation: male gender (7:1 compared to females), African American, prolonged dialysis, severe ACKD with marked kidney enlargement

Management: surveillance imaging studies per symptoms and patient life expectancy:

- Low life expectancy: no screening
- Good life expectancy: yearly kidney ultrasound (some experts suggest annual follow-up if one or more cysts >3 cm not meeting criteria for resection and every 3 years if smaller cysts)
- In the presence of hematuria, flank pain, unexplained fevers, erythrocytosis, and/or unexplained worsening BP, obtain an immediate kidney ultrasound and consider CT urogram. See **Chapter 6: Tubular, Interstitial, and Cystic Disorders** for interpretation of imaging studies.
- ACKD may regress to some degree with a successful kidney transplant.

Malnutrition

Malnutrition adversely affects survival in ESKD.

Contributing factors

- Poor appetite, inappropriate protein restriction
- Increased inflammatory state
- Poor GI absorption (eg, gastroparesis, nausea, vomiting)
- Increased albumin loss with PD
- Inadequate dialysis dose

Global assessment of malnutrition

- BMI
  - Individuals with higher BMI (ie, >25 kg/m^2) generally have better survival compared with their counterparts with normal or low BMI.
  - Survival advantage of higher BMI may more specifically pertain to patients older than 65 years and not necessarily younger patients.
  - Cause of death is more commonly due to CV events in patients with higher BMI and noncardiovascular etiology in those with lower BMI.
- Anthropometric measurements (eg, skin-fold thickness, limb circumference)

Biomarkers for both nutritional and inflammatory status

- Lower albumin level is a strong predictor of mortality in dialysis patients.
- Total iron binding capacity is reduced in inflammatory states.
- C-reactive protein level is increased in inflammatory states.

Malnutrition-inflammation complex syndrome (a.k.a. protein-energy wasting syndrome)

- Concurrent malnutrition and inflammation
- Prevalence is up to 70% in dialysis patients.

- May arise from poor dietary intake, coexisting illnesses, genetic susceptibility, dialysis procedures, infections

Management

- Collaboration between a registered dietician nutritionist and a physician or other health care provider to provide medical nutrition therapy is recommended.
- Protein supplements (eg, 14-20 g 3 times weekly) given to patients with serum albumin less than 3.5 g/dL has been shown to improve hospitalization and survival rates.
- Nutritional recommendations per KDOQI (**Table 4.5**)

Table 4.5 Nutrition guidelines per KDIGO

Daily intake	Pre-ESKD	Pre-ESKD with DM	Hemodialysis	Peritoneal dialysis	HD or PD with DM
Energy (kcal/kg) <60 y	35	35	35	35	—
Energy (kcal/kg) >60 y	30-35	30-35	30-35	30-35	—
Protein (g/kg dry BW)	0.55-0.60 or 0.28-0.43 dietary protein/kg/d plus ketoacid analogs to meet 0.55-0.60 g/kg/d protein requirements	0.8-0.9 g/kg/d	1.0-1.2	1.2-1.3	1.0-1.2
Sodium	<90 mmol/d (2.0 g) to reduce blood pressure ± proteinuria and minimize volume overload				

Daily intake	Pre-ESKD	Pre-ESKD with DM	Hemodialysis	Peritoneal dialysis	HD or PD with DM
Potassium	Adjust dietary intake as needed to maintain normal serum potassium level.				
Phosphorus	Adjust dietary intake to maintain normal serum phosphate level. See text for best food source.				
Calcium	Total elemental Ca^{2+} intake of 800-1000 mg/d (including dietary intake, supplement, Ca^{2+}-based phosphate binders) to maintain neutral Ca^{2+} balance.		Adjust calcium intake to maintain normocalcemia (given possibility of concurrent use of vitamin D analogs or calcimimetics).		
Dietary patterns	Advise Mediterranean diet in adults with CKD 1-5 and posttransplant with or without dyslipidemia. For CKD G1-G4, a diet with increased fruit and vegetable may decrease BW, BP, and net acid production.				
Others	LC n-3 PUFA ~2 g/d may be prescribed to improve triglyceride levels.		LC n-3 PUFA 1.3-4 g/d may be prescribed to reduce triglycerides and LDL cholesterol and raise HDL levels.		
Multivitamins			It is reasonable to consider MVI in adults with CKD 5D and evidence of prolonged inadequate dietary intake.		
Folic acid	Routine supplementation ± B-complex is not recommended due to lack of beneficial CV outcomes.				
Vitamin C	It is reasonable to consider supplementation to meet recommended intake of >90 mg/d for men and 75 mg/d for women. Avoid excessive intake due to risk of calcium oxalate precipitation.				

Daily intake	Pre-ESKD	Pre-ESKD with DM	Hemodialysis	Peritoneal dialysis	HD or PD with DM
Vitamin D	Vitamin D supplementation with cholecalciferol or ergocalciferol to correct 25(OH)D deficiency/insufficiency is suggested.				
Vitamins E, A	Routine supplementation is not suggested due to potential for vitamin toxicity.				
Selenium, zinc	Routine supplementation is not suggested due to lack of evidence for benefits.				

Abbreviations: 25(OH)D, 25-hydroxylated vitamin D; BP, blood pressure; BW, body weight; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; ESKD, end-stage kidney disease; HD, hemodialysis; HDL, high-density lipoprotein; KDIGO, Kidney Disease Improving Global Outcomes; LC n-3 PUFA, long chain omega-3 polyunsaturated fatty acid; LDL, low-density lipoprotein; MVI, multivitamins; PD, peritoneal dialysis.

Neuropsychiatric Complications of CKD

Depression

- Most common psychiatric disorder in chronic dialysis patients
- Most common psychiatric disorder requiring hospitalization in dialysis patients
- Correlates with a 30% or more increase in mortality
- Risk for increased CVD and mortality
- Risks: younger age, patients with lower SCr and albumin
- Routine screening recommended at first dialysis, biannually, or more as needed
- Treatment: antidepressants, psychiatric referral. Most antidepressants are hepatically metabolized and do not require dose adjustment with the exceptions of paroxetine and venlafaxine.

Sleep disorders

Poor sleeping score is associated with an increased relative risk of death of approximately 1.3 (Dialysis Outcomes and Practice Patterns study or DOPPS).

Insomnia

- Most common sleep disorder in dialysis patients (prevalence up to 70%)
- Insomnia is associated with restless leg syndrome (RLS), depression, and pain, and vice versa.

Sleep apnea

- Prevalence up to 50% compared to less than 5% in general population
- Pathogenesis: fluid overload with upper airway congestion "rostral fluid shift" during sleep, uremia-induced alteration in central ventilator control, presence of comorbid conditions
- Nocturnal arterial oxygen desaturation is associated with higher CV events and worse survival in HD patients.
- Compared to conventional HD, daily nocturnal HD (nHD) reduces the apnea-hypopnea index (episodes of apnea per hour of sleep).
- Treatment of sleep apnea improves survival.

Uremic polyneuropathy (UPN)

- UPN is a distal symmetric sensorimotor polyneuropathy that typically affects lower limbs but may spread to upper limbs.
- UPN is characterized by demyelination of large nerve fibers, leading to axonal degeneration.
- Occurs in 60% to 100% of patients with CKD and ESKD, may be more common in males

Possible contributing factors

- Deficiencies in thiamine, zinc, and biotin and decreased transketolase activity
- Accumulation of phenols, myoinositol, β2-microglobulin, and other uremic "middle-molecular-weight molecules"

- Others: hPTH, electrolyte disturbances, particularly dyskalemias

Clinical manifestations

- May be asymptomatic until GFR less than 15%
- Both slowly and rapidly progressive disease may occur, the latter in association with acute illnesses, such as sepsis.
- Symptoms: typically, slowly progressive sensorimotor axonal neuropathy, which advances proximally, starting from lower limbs with possible spread to upper limbs; paresthesia, numbness, hyperesthesia to noxious stimuli, thermal sensitivity impairment, restless legs, cramps, impaired deep tendon reflexes, weakness, imbalance, lower limb atrophy, optic neuritis (sudden vision deterioration, blurry vision), autonomic dysfunction with orthostatic hypotension and dizziness
- In contrast, diabetic neuropathy is a slow and progressive condition that is primarily associated with sensory deficit in a "stock-and-glove" distribution.

Risks: DM, advanced age, advanced CKD, dialysis vintage

Diagnosis

- Nerve conduction study revealing severe reduction in nerve conduction velocity
- Loss of light touch and vibratory perception in toes, decreased deep tendon reflexes (eg, Achilles reflex), muscle atrophy in severe and prolonged cases

Management: Optimize/intensify dialysis dose, use of high-flux membrane, gabapentin, tricyclic antidepressants, biotin supplementation, symptomatic relief (see restless leg syndrome below), and kidney transplant may reverse UPN.

Restless leg syndrome (RLS)

- RLS is characterized as an unpleasant sensation in the lower extremities with the compulsive need to move the legs, is worse in the evening, and improves with walking.
- The incidence is reported to be up to 60%.

- RLS is associated with a higher risk for CV events *and* mortality.

Contributing factors

- Reduced dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and resultant spinal cord excitability
- Iron (Fe) deficiency: Fe is a cofactor for tyrosine hydroxylase, the rate-limiting step in the synthesis of dopamine.
- Others: altered calcium/phosphate metabolism, hyperhomocysteinemia, anemia, sympathetic nervous system activation, peripheral neuropathy

Treatment options

- Iron supplementation if deficient
- Dopamine receptor agonists such as pramipexole, ropinirole, or rotigotine, levodopa plus decarboxylase inhibitors (Sinemet). Monitor for impulse control disorders and "augmentation," that is, worsening of symptom severity while on dopaminergic medication.
- Gabapentinoids: gabapentin or pregabalin (renal dose adjustment is required)
- Others: opioids, benzodiazepines, aerobic exercise, avoidance of caffeine, alcohol, and nicotine at bedtime. Optimize dialysis treatment if applicable. Concomitant use of gabapentin or pregabalin and drugs that depress the central nervous system (CNS) should be avoided.

Bleeding Diathesis in CKD/ESKD

Contributing factors

- Platelet dysfunction
- Uremic toxins (eg, urea, guanidinosuccinic acid, phenolic acid, methylguanidine) may interfere with adenosine diphosphate (ADP)-induced platelet aggregation and thromboxane A_2 (thromboxane A_2 increases platelet aggregation).

- Anemia
  - Dilutional effect of platelets with reduced RBC mass
  - RBCs bind NO. With anemia, increased free NO stimulates *cyclic guanosine monophosphate* (cGMP) production with subsequent suppression of thromboxane A_2 and ADP production. RBCs also release thromboxane A_2 and ADP.
- EPO deficiency: EPO increases platelet production.
- von Willebrand factor (vWF) abnormalities
- Vessel abnormalities resulting in ineffective vasoconstriction

Corrective options

Blood transfusion: Blood transfusion for urgent high risk of bleeding surgeries to achieve Hb approximately 10 g/dL has been suggested for individuals with Hb less than 9 g/dL (Grade 2C).
ESA: ESA administration requires approximately 7 days to increase platelet count and function.
Dialysis

- Both HD and PD can improve bleeding time.
- Mechanism is thought to be via removal of uremic toxins.
- If dialysis is performed prior to surgery, avoid using systemic anticoagulants.

DDAVP

- Rapid (within an hour) onset of action with endothelial release of factor VIII and vWF
- 0.3 µg/kg IV administered over 30 minutes
- Therapeutic effect of DDAVP is approximately 24 hours and becomes refractory within 48 hours due to depletion of stored factors.
- Use with great caution in patients with increased risks for CVDs and HF due to potential rapid changes in BP and heart rate.
- Hyponatremia may be a complication with ad lib water intake.

Cryoprecipitate

- Administer 10 units IV
- Immediate onset of action, duration of action 4 to 12 hours
- Contains factors VIII and XIII, vWF, fibrinogen, and other clotting factors

Conjugated estrogen

- Onset of action 6 hours to 5 to 7 days, duration of action 2 to 3 weeks
- Mechanism of action: decreases L-arginine production (NO precursor), decreases antithrombin III and protein S levels, increases factor VII

Other CKD-Related Issues

Nephrogenic systemic fibrosis (NSF)

NSF is a debilitating and potentially fatal scleroderma-like condition associated with the use of gadolinium (Gd) in patients with advanced CKD or receiving any dialysis modality.

Clinical manifestations: painful, symmetric erythema and edema that become firm papules/plaques and nodules resembling burn scars. Internal organ fibrosis may occur.

Pathogenesis: increased production and migration of circulating fibrocytes to susceptible tissues with ongoing inflammation or injury

Risk factors: reduced eGFR less than 15 to 30 mL/min/1.73 m^2 (AKI or CKD), use of group I Gd (see below), PD may have increased risk compared with HD, elevated serum phosphate levels, exposure to high dose or repeated exposures

Triggering factors: underlying ischemic or thrombotic vascular injury, infection, high-dose EPO therapy

Gd group and risk for NSF

- Group I: agents with highest number of NSF reported (eg, Omniscan, Magnevist, OptiMark)
- Group II: agents with few or no unconfounded cases of NSF (eg, MultiHance, Gadavist, Dotaram, ProHance)

- Group III: agents with limited number of administrations but with no NSF reported (eg, Ablavar, Eovist)

General suggestions

- For eGFR 30 mL/min/1.73 m^2 or more, Gd agent from any group may be used.
- For non–dialysis-dependent individuals with eGFR less than 30 mL/min/1.73 m^2, offer Gd agent from group II or III. Do not use agent from group I.
- For dialysis-dependent individuals, avoid Gd if possible. Review indications and alternative options with institutional radiologist. If Gd must be used, avoid group I agent. Risks and benefits must be weighed and explained to patients.

Management

- Avoidance of Gd agents with highest number of NSF reported in patients with GFR less than 30 mL/min or AKI. Check with institutional radiologist for best agent used.
- Beneficial medical therapies reported: corticosteroids, sirolimus, PTF, methotrexate, high-dose IV immunoglobulin, imatinib mesylate, sodium thiosulfate
- Other reported beneficial interventions: successful renal transplant, ultraviolet A phototherapy, plasmapheresis

KDIGO immunization recommendations for patients with CKD

- Annual influenza vaccine should be given if not contraindicated.
- Polyvalent pneumococcal vaccine (PCV) for all adult patients with CKD, regardless of the stage if no contraindication
- Hepatitis B vaccine for all adults with eGFR less than 30 mL/min/1.73 m^2 and those with high risk of CKD progression. Confirm response serology. Antibody titer above 10 confers immunity.
- Others per routine: tetanus, diphtheria, pertussis (Td/Tdap), varicella, human papillomavirus, zoster, measles, mumps, rubella

(MMR)

- COVID-19 vaccines are recommended for patients with CKD. Schedule varies per formulation: National Kidney Foundation. COVID-19 vaccine and treatments for people with kidney disease. Accessed July 15, 2024. https://kidney.org/coronavirus/vaccines
- See **Chapter 9: Kidney Transplantation**. Live vaccines are contraindicated post-transplantation.

STAGES IV AND V CKD

Preparation for End Stage Kidney Disease (ESKD) (KDOQI)

- All patients reaching CKD G4/G4T with progressive decline in kidney function should be educated on all modalities of kidney replacement options, including kidney transplantation. Family members and/or caretakers should also be educated about the process.
- KRT modality selection depends on goals of care, local resources, capacities of regional health care facilities, family/social support, and patient's own cost of care, level of independence/dependence, preservation of residual kidney function, and underlying medical conditions.

Dialysis access preparation

PD access

- PD catheter should be placed whenever possible at least 2 weeks prior to KRT.
- Urgent start PD may be an option if medically safe and performed properly.

HD vascular access

- KDOQI: Referral for surgical evaluation and creation of a new arteriovenous (AV) access should be done at eGFR 15 to 20 mL/min/1.73 m^2 or earlier in patients with unstable and/or eGFR decline of greater than 10 mL/min/1.73 m^2/y.
- Type of access depends on:

- Remaining life expectancy (eg, permacath may be reasonable if life expectancy is less than a year, whereas arteriovenous fistula [AVF] or arteriovenous graft [AVG] is preferred in patients with longer life expectancy)
- Quality of blood vessels
  - Whole arm rather than finger exercise is recommended following AVF creation.
  - KDOQI does not suggest the use of heparin, clopidogrel monotherapy, glyceryl-trinitrate, cholecalciferol, or clopidogrel-prostacyclin for AVF maturation or improvement of primary/secondary patency.

Timing for dialysis initiation

IDEAL trial: There is no survival benefit between early versus late start (initiate HD at eGFR 10-15 vs 5.0-7.0 mL/min/1.73 m^2) if patient can tolerate late start (absence of uremic symptoms or complications associated with ESKD).

KDOQI 2015: The decision to initiate maintenance dialysis should be based primarily on signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to medically manage metabolic abnormalities and/or volume overload safely rather than on a specific level of kidney function.

Uremic Signs and Symptoms

- Recurring hyperkalemia despite corrections of all contributing factors
- Volume overload leading to pulmonary edema or refractory to diuretics
- Uremic pericarditis, unexplained pericardial effusion
- Nausea/vomiting
- Severe metabolic acidosis, particularly if cannot tolerate oral alkalinization
- Declining health due to uremia
- Malnutrition:

- General indicators: decline in serum albumin, weight loss
- Patients with less than 90% of standard body weight (SBW) are considered to be mildly to moderately malnourished, and those who are less than 70% of SBW are considered severely malnourished. It is recommended that a target body weight for maintenance dialysis patients be between 90% and 110% of SBW (NHANES III).

Patient preference for a trial of medical nondialytic management prior to dialysis initiation should be considered when the patient is medically stable and asymptomatic.

For patients older than 60 years

- In the absence of AKI/illnesses, delay in dialysis initiation until eGFR less than 6 mL/min/1.73 m^2 may be acceptable. GFR decline may be relatively slow in this population.
- 20% to 35% of older CKD G4 to G5 die per year prior to reaching dialysis.
- Older patients have a lower likelihood of survival in the 90 days following dialysis initiation.

Other considerations for KRT initiation

- Consider the use of risk equations for predicting time frame to needing KRT.
- Criteria for dialysis initiation for failed transplant recipients are similar to those with ESKD of native kidneys.

Planning for end-of-life care or withdrawal of KRT (Renal Association 2014)

- Estimate and discuss with patients regarding prognosis and quality of life both with and without KRT.
- Patients with deteriorating conditions/comorbidities despite dialysis should be given consideration for end-of-life care.
- For patients with poor life expectancy, maintain a supportive care registry to ensure care needs are met and provide opportunity for advance care planning.

- Dialysis withdrawal should include end-of-life care planning by patient and all involved health care professionals. Assessment for competence and evaluation for depression should be performed.

Indications for dialysis withdrawal

- Patients in any state of health with full decision-making capacity and absence of depression who choose to withdraw from dialysis. This is consistent with the law that upholds any competent adult's right to decline medical care.
- Patients with irreversible mental incapacitation where dialysis cannot be safely administered
- Patients with terminal conditions despite intensive therapy where dialysis not only minimally prolongs life but also prolongs suffering
- Patients with limited life expectancy (ie, expected death within 60 days) where dialysis is not expected to change outcome

Palliative care for patients with ESKD without dialysis support

- Prognosis after dialysis withdrawal: Survival depends on residual kidney function.
- Consult palliative care and plan for hospice care.
- Symptomatic relief:
  - Neurologic manifestations:
    - Anxiety, agitation, delirium: Review and remove any medications that may be contributory, consider benzodiazepines with or without haloperidol (dose adjust haloperidol to avoid extrapyramidal symptoms).
    - Pain: Evaluate for reversible source and type of pain and treat accordingly. If necessary, provide opioids as needed. Opioids that are safer for patients with advanced CKD include fentanyl, buprenorphine, methadone, or hydromorphone. Start at lowest doses and uptitrate as needed. Note that morphine and its metabolites are

neurotoxic and can cause altered mental status and seizures.
    - Myoclonus and seizures: benzodiazepines
- Respiratory symptoms:
    - Short of breath, dyspnea: Avoid excessive fluid intake, consider "palliative dialysis" for fluid removal only, consider opioids in terminal illness, provide supplemental oxygen, keep head of bed elevated.
    - Respiratory tract secretions with gurgling sound: If patient is unresponsive, assure family that the patient is not suffering. Provide diuretics if the patient still has residual kidney function; otherwise, consider using an anticholinergic agent, such as glycopyrrolate.
- GI symptoms:
    - Nausea/vomiting: metoclopramide (if delayed gastric emptying), ondansetron
    - Constipation: stool softeners and laxatives, particularly for patients taking opioids
- Skin: Use moisturizers. In severe uremic pruritis, consider gabapentin, pregabalin, or the κ-receptor agonist difelikefalin.

END-STAGE KIDNEY DISEASE (ESKD)

U.S. Policies in the Care of ESKD

- In 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) launched the prospective payment system (PPS) for ESKD care, when the "bundled" payment system was created.
- In July 2019, the Center for Medicare and Medicaid Innovation's Advancing American Kidney Care aimed to improve CKD and ESKD outcomes.

See **Appendix A4.3** for U.S. policies in the care of patients with ESKD.

Factors Associated With Worse Survival in the Dialysis Patient

Patient factors: Caucasians have decreased survival compared to Blacks, poor nutritional status (lower serum albumin, lower cholesterol levels, lower BMI), presence of inflammation or high inflammatory markers (higher C-reactive peptide levels), troponin leaks, lower predialysis serum potassium levels, poor control of MBD, depression, sleep apnea, RLS, loss of residual kidney function. The presence of residual kidney function has been suggested to improve both CV events and mortality.

Dialysis factors: (highest death rates on) Sunday evening/Monday for Monday/Wednesday/Friday HD patients and Monday evening/Tuesdays for Tuesday/Thursday/Saturday dialysis patients (presumably due to CV complications/volume overload/electrolyte abnormalities), use of dialysate K^+ concentration less than 2 mEq/L, lower dialysis duration, higher UF rate (ie, >13 mL/kg/h), intradialytic myocardial stunning (measured as intradialytic regional wall motion abnormalities; higher risk of myocardial stunning with higher UF and intradialytic hypotensive episodes)

Hemodialysis

Solute clearance

- Diffusion is determined by the concentration difference between blood and dialysate.
- Convection, a.k.a. "solvent drag," occurs with UF where smaller solutes are "dragged" by the movement of water across the dialysis membrane.
- HD relies mostly on diffusion for solute clearance.

Hemodialyzers

Dialyzer membrane type

- Membrane used for dialysis is made of substituted cellulose, cellulosynthetics, or synthetics.
- The frequency of complement activation occurs in the following order: cellulose > substituted cellulose, cellulosynthetic > synthetic. Membranes with high degree of complement activation induce more problems with anaphylactic shock or nonspecific allergic reactions to patients. Cellulose membranes are no longer used.

Membrane resistance: Resistance for solute movement across membrane depends on membrane thickness and unstirred fluid layers next to the membrane.

Membrane pore size

- Type/size of solute removal depends on pore size of membrane.
- Membranes with larger pore size provide "higher flux" dialysis.

UF coefficient (Kuf)

- K_{uf} typically ranges from 3.3 to 83 mL/h/mm Hg.
- Higher K_{uf} provides greater dialysis efficiency and flux. The former is due to increased "solvent drag" from convection.
- Use lower transmembrane pressure (TMP) for membranes with higher K_{uf} to achieve the same volume of UF. UF volume = K_{uf} × TMP

Example: What should the TMP be to remove 500 mL/h for membranes given known K_{uf} (know how to calculate TMP or UF volume from K_{uf})?

Given K_{uf} of 50 mL/h/mm Hg: TMP = 500 mL/h ÷ 50 mL/h/mm Hg = 10 mm Hg

Mass transfer coefficient for urea: KoA urea (maximum theoretical clearance): 245 to 1,000^{+} mL/min (<500 "low efficiency," 500-700 "moderate efficiency," >700 "high efficiency")

Surface area of dialysis membrane: The larger the surface area, the greater the dialysis efficiency.

Factors that determine HD efficiency:

- The greater the following factors, the greater the "hemodialysis efficiency":
  - Membrane surface area
  - KoA and K_{uf} of membrane
  - Duration of dialysis
  - Dialysate flow rate (Q_d)
  - Blood flow rate (Q_b)
  - Vascular access flow (Q_a)
  - Concentration gradient difference of solute between dialysate and blood
- Dialysis efficiency is *not* dependent on dialyzer membrane type, but rather the membrane's KoA, K_{uf}, and surface area.
- Scenarios with reduced dialysis efficiency:
  - Access recirculation reduces dialysis efficiency.
  - For central venous catheters (CVCs), cardiopulmonary recirculation is higher in patients with lower cardiac output (CO), thus lower dialysis efficiency.

High efficiency versus high flux and super high-flux HD

- High efficiency HD refers to dialyzing through standard cellulosic membranes with large surface areas.
- High-flux and super high-flux HD refer to performing HD using noncellulosic membranes with larger porosity, hence increased permeability to large middle molecules, such as β2-microglobulin. Advantages of high-flux and super high-flux over low-flux HD may include:
  - Improved β2-microglobulin clearance, thus potential reduction in late amyloid deposition
  - Improved lipid abnormalities
  - Lower inflammatory response by neutrophils and monocytes
  - Possible improved mortality compared with low-flux HD

Expanded hemodialysis (HDx)

- HDx was designed to increase the effectiveness of HD by improving the removal of large middle molecules without causing significant hypoalbuminemia using the medium cutoff (MCO) membrane, a.k.a. the high retention onset membrane.
- Compared with conventional membranes including high-flux membranes, the MCO membrane is considered to be closest to the physiology of the glomerular filtration barrier.
- Several studies have shown the use of the MCO membrane in HDx confers clinical benefits and better outcome (eg, lower all-cause hospitalizations, medication usage, cost of care). Further studies are needed to assess long-term effects.

Reuse of dialyzers: No increase in mortality has been shown with dialyzer reuse compared with single-use dialyzers if reuse protocols are strictly followed. Risks of reuse: infections, exposure to disinfectants, loss of membrane integrity and function.
For other common terms used in HD, see **Appendix A4.4**.

Dialysate for HD

Sodium

- Sodium modeling: Using dialysate [Na^+] greater than that of patient's plasma minimizes intradialytic hypotension and symptoms of disequilibrium at the expense of sodium gain, increased thirst, increased interdialytic weight gain (IDWG), and predialysis HTN. Sodium modeling has fallen out of favor due to these side effects.
- DOPPS: Patients with serum [Na^+] less than 137 mEq/L appear to have survival benefits when higher dialysate [Na^+] (>140 mEq/L) was used. Similar findings were not appreciated in patients with higher S[Na^+].
- Using dialysate [Na^+] lower (eg, 5%) than that of patient's plasma can improve UF to achieve dry weight (as a temporary measure) (DOPPS).

Potassium

- There is a theoretical concern that rapid change in plasma potassium (ie, use of much lower dialysate [K^+] compared to patient's plasma level) may induce arrhythmias.
- This concern remains to be proven. Nonetheless, there are data to suggest an increased risk of sudden cardiac death with the use of dialysate [K^+] less than 2 mEq/L for patients with S[K^+] less than 6.5 mEq/L.

Calcium

- Ideal dialysate calcium concentration is 2.5 to 2.75 mEq/L.
- Lower dialysate calcium concentration is associated with an increased risk for cardiac arrest, intradialytic hypotension, and secondary hPTH.
- Higher dialysate calcium concentration may lead to increased vascular and soft tissue calcifications.

Bicarbonate

- HD patients with serum bicarbonate concentration less than 22 mEq/L have an increased risk of all-cause and CV mortality compared to those with levels 24 to 25 mEq/L.
- Predialysis serum bicarbonate concentration greater than 27 mEq/L is also associated with higher risk of death. Bottom line: Keep goal serum bicarbonate between 22 and 27 mEq/L.

HD adequacy and prescription

Adequacy and prescription

- Traditionally, adequacy refers to small solute clearance (Kt/*V* and urea reduction ratio [URR] in HD and Kt/*V* and urea clearance in PD). See **Appendix A4.5** for explanation of Kt/*V*. The clinical significance of this concept is being questioned as evidence for the relationship between small solute clearance and clinical outcomes is weak. Future direction may move toward "goal-directed dialysis care" rather than just small solute clearance. In essence, in addition to measuring small solute clearance, factors such as residual kidney function, volume status, biochemical

measures, nutritional status, CV function, symptoms, and patient's experiences and goals will also be considered. Dialysis adequacy herein refers solely to small solute clearance as traditionally defined.

- Other concerns with Kt/*V*:
  - Current Kt/*V* target dosing may not be adequate in women or small patients.
  - Single-pool Kt/*V* (spKt/*V*), where *V* is based on the volume of distribution of urea or total body volume, is not associated with improved survival, whereas higher Kt/*V* normalized for BSA Kt/*V* is associated with survival benefit.

spKt/V versus equilibrated Kt/V (eKt/V)

- spKt/*V* is a non-equilibrated Kt/*V*, measured by slowing blood pump to 100 mL/min for 15 seconds and then stop the pump prior to BUN sampling. Slowing the blood flow to 100 mL/min reduces the entry of dialyzed blood into the access and stops cardiopulmonary and HD access recirculation. spKt/*V* measures clearance from a single treatment and does not capture missed HD sessions.
- eKt/*V*, a.k.a. double-pool Kt/*V*, measures BUN 30 minutes following the completion of HD to allow for dissipation of HD access and cardiopulmonary recirculation and equilibration of urea from the extravascular into the vascular compartment. For these reasons, eKt/*V* is typically lower than spKt/*V* by approximately 0.21.

KDOQI recommendations for HD adequacy given 3 times per week

- For patients with residual kidney urea clearance K_r less than 2 mL/min/1.73 m^2:
  - Minimally adequate dose: spKt/*V* 1.2 or higher per dialysis (not including K_r), or URR 65% or more
  - Target dose: spKt/*V* 1.4 or higher (~eKt/*V* ≥1.2) per dialysis (not including K_r), or URR 70% or more

- For patients with residual kidney urea clearance K_r 2 mL/min/1.73 m^2 or more
  - Minimally adequate dose: spKt/*V* may be lower than 1.2.
  - Target dose: 15% or more of minimum dose
- The CMS conditions for coverage for ESKD require maintenance of spKt/*V* of at least 1.2.
- Targeting Kt/*V* greater than 1.4 does not appear to improve survival or reduce hospitalization rates.

Dialysis duration

- Optimal dialysis time and frequency are undefined. The 2015 KDOQI clinical practice guideline recommends greater than 3 hours for patients who receive HD 3 times a week. Some experts suggest 4 hours or more.
- Dialysis session duration less than 4 hours has been associated with increased mortality and morbidity.
- Frequent HD has been suggested for patients with nutritional problems or volume overload, but current data show no benefit in terms of improved nutritional status or anemia control.

UF rate

UF rate greater than 13 mL/kg/h is associated with increased mortality. UF rate less than 10 mL/kg/h is suggested.

Non-in-center HD

Nocturnal HD (nHD)

- Potential benefits:
  - nHD is associated with lower IDWG, better serum albumin and phosphorus levels, WBC count, and SBP compared with matched control from in-center HD patients. There is also increasing evidence of regression of LVH with nHD.
  - Survival benefits are conflicting.
- Potential problems: high dropout rate, higher vascular access complications compared to in-center HD, faster loss of residual

kidney function, increased caregiver burden

Home hemodialysis (HHD)

- Patient selection: Psychosocial and medical evaluations and home environment assessment are required.
- HHD training
  - HHD training programs generally range from 3 to 8 weeks.
  - Vascular access training
    - Cannulation by either patient or partner/caregiver
    - Recognition of vascular access infection and dysfunction
- Dialysis prescriptions and clinical outcomes
  - Low dialysate flow and short daily HD treatments are typically used.
  - Goal-directed prescription: Modify prescription to achieve goals and clinical outcomes.
- Advantages of HHD:
  - Flexibility to modify dialysis prescription in terms of frequency and duration
  - High-intensity HD (ie, ≥5 times a week, 6-8 hours per session) is associated with stabilization of LV remodeling, regression of LVH, improved BP control and LV function, correction of ESKD-associated obstructive sleep apnea, improved metabolic and volume control without dietary restriction, improved maternal and fetal outcomes in pregnancy, and improved survival compared with traditional 3 times per week HD.

HD Vascular Access

Vascular access goal for chronic HD: AVF 60%, AVG 30%, temporary CVC less than 10%

Acute temporary catheters or cuffed tunneled catheter (permacath)

- KDOQI: When there are valid reasons for CVC use and duration of use is expected to be greater than 3 months, without anticipated availability of AV access, CVC may be placed in the following veins in order of preference: right internal jugular (IJ) > left IJ > external jugular > femoral > subclavian > lumbar/transhepatic
- CVC have low-flow rates (300 mL/min for temporary catheters, 400 mL/min for permacath).
- Catheter positioning
  - Nontunneled IJ HD catheters should be positioned in the distal superior vena cava (SVC). Avoid atrial placement due to the stiffness of short-term access catheters.
  - Tunneled HD catheters should be positioned within the right atrium when the patient is in supine position. Catheters retract with standing.
  - Femoral HD catheters should be placed in the inferior vena cava (IVC).
- Promote "Choosing Wisely" campaign in patients with CKD/ESKD to "save the vein" and avoid peripherally inserted central catheter (PICC) lines whenever possible.

Access infections

- Higher rates for infections compared to AVG and AVF
- Predominant pathogens: *Staphylococcus aureus* and *Staphylococcus epidermidis*
- Femoral lines are not at increased risk for infections unless patients have markedly elevated BMI.

Access solute clearance (URR)

- Femoral access placement is an acceptable alternative to the right jugular vein in critically ill patients.
- Femoral catheters should be long enough (typically >20 cm) to reach the IVC for better clearance.
- For blood flow greater than 200 mL/min, URR is lower in femoral compared with jugular.

Arteriovenous fistula

- Preferred access due to lower risk of infectious and thrombotic complications
- High rate of primary failure (nonmaturation), but better long-term patency compared to grafts

Preoperative vascular mapping increases fistula placement but fails to improve primary failure (nonmaturation). Optimal venous mapping findings:

- Arterial diameter 2.0 mm or longer, vein diameter 2.5 mm or longer
- Brachial artery flow greater than 80 mL/min
- Absence of stenosis or thrombosis of draining vein up to shoulder and central vein

Clinical risks for AVF nonmaturation: older age, females, peripheral vascular disease, prior PICC line, forearm compared with upper arm AVF

Optimizing AVF maturation success

- 6-Week postoperative ultrasound: vein depth less than 5.0 mm, vein diameter longer than 4.0 mm, length of fistula thrill/bruit longer than 5.0 cm, access flow greater than 500 mL/min ("Rule of 5")
- There is inadequate evidence to make recommendations on the use of simvastatin/ezetimibe to reduce AVF dysfunction or clopidogrel-prostacyclin to improve AVF primary failure.

Early surgical repair

- Vein is too deep: repair by superficialization
- Low access flow:
  - Due to stenosis at anastomosis or draining vein: repair by angioplasty or surgical revision
  - Due to large accessory veins: repair by surgical ligation

Risks for secondary AVF failure: intradialytic hypotension, frequent cannulation rate (ie, daily HD)

Arteriovenous graft

- May be considered in patients with suboptimal venous mapping parameters, failed AVF, or low expected patient survival
- Synthetic conduit (eg, polytetrafluoroethylene) created between an artery and a vein
- AVG maturation typically requires 2 to 3 weeks. However, Vectra or Flixene grafts may be used in 12 hours.

Potential complications

- AVG thrombosis and stenosis at anastomotic site, draining vein, or central veins
- AVG has higher infection risks compared to AVF. Infectious lesions that involve the underlying AVG require complete surgical resection.
- Pseudoaneurysms caused by repeated cannulations at the same site of the AVG may result in life-threatening bleeding and must be repaired surgically or with covered stent placement.

Potential complications of either AVF or AVG

Dialysis access steal syndrome refers to decreased blood flow to the distal extremity due to increased blood flow through the AV access.

- Patients typically present with hand pain, coolness, and reduced sensory and motor function.
- Treatment options: AV access ligation for severe ischemia, banding to reduce flow in the high-flow AV access, or vascular repair to improve distal blood flow in the low- or normal-flow AV access

Ischemic monomelic neuropathy (IMN) is a rare variant of access steal syndrome where patients present with severe hand pain due predominantly to nerve ischemia. AV access ligation is recommended for this complication.

Improving graft patency

Anticoagulation for protection against graft thrombosis and survival: KDOQI 2019 Update recommends against systemic anticoagulation for the sole purpose of maintaining CVC patency.

Vascular access use and monitoring

- Rope-ladder technique refers to rotating cannulation sites for HD access.
- Buttonhole technique refers to cannulation at the same site for HD access.
- Rope-ladder cannulation is "recommended" over buttonhole technique for AVF and "suggested" for polytetrafluoroethylene grafts.
- Buttonhole technique is presumed to be easier with lower pain scores with prolonged use due to the development of a skin tract or buttonhole. However, it may be associated with an increased risk of infection due to poor cleaning techniques and/or failure to remove scab prior to cannulation.
- Regular physical examination to detect flow dysfunction is recommended. (Clinical clues for AV access stenosis: prolonged bleeding, unexpected fall in Kt/*V*, distal edema, abnormal bruits or reduced thrill)
- Routine AVG and AVF surveillance by measuring access blood flow, pressure monitoring, or imaging for stenosis is not suggested. Doppler findings of reduced blood flow, defined as less than 600 mL/min or fall by more than 25% from baseline, suggest significant stenosis.

Water Treatment for HD

- On average, weekly HD requires approximately 500 L of H_2O (assuming an average dialysate flow of 800 mL/min, 3-4 h/dialysis treatment, three treatments per week).
- Water purification steps: *Required steps* include carbon filtration and reverse osmosis.

Carbon filtration

- Removes chlorine and chloramine (added to municipal water) and organic contaminants. Chloramine can cause hemolysis.
- Carbon filtration is done prior to reverse osmosis (see below) because chlorine and chloramine can damage the membrane used in reverse osmosis.

Softeners (optional if hard water to protect reverse osmosis membrane)

- Exchanges calcium and magnesium ions for sodium ions
- This step may be added prior to reverse osmosis to protect the reverse osmosis membrane. Accumulation of calcium and magnesium can cause fouling of osmosis membrane.

Reverse osmosis

- A process whereby water is forced across a semipermeable membrane by a high-pressure system
- Reverse osmosis removes dissolved inorganic elements including metal ions (ie, zinc, fluoride, copper, aluminum, arsenic), salts, chemicals, organic elements, bacteria, viruses, and endotoxins.

Deionization

- Further removes residual ions by exchange resins made up of both cations and anions (eg, hydrogen and hydroxyl ions, respectively) to exchange for negatively and positively charged ionic contaminants respectively following reverse osmosis
- Close monitoring of the product's water-specific resistivity or conductivity is required to detect changes consistent with depletion of resins. Depletion of resins can cause release of previously removed ions such as *fluoride and may result in acute toxicity and death*. Chronic fluoride exposure can contribute to osteodystrophy.

- Note that the deionizer provides a good milieu for bacterial proliferation. An extra step for bacterial control is needed.

Ultrafilter/endotoxin filter

This is an optional step used to remove any residual bacteria and endotoxins.

Microbiologic testing

Routine microbiologic testing must be performed for both bacterial count (<100 colony-forming unit [CFU]/mL) and endotoxins (<0.5 EU/mL). Corrective measures must be done at half of maximal allowable levels. Water purification for dialysis does not produce "sterile" water.

Hospital bedside and HHD water purification

- Water treatment approach is similar to outpatient fixed-station systems.
- Mobile units similarly require a carbon filtration, reverse osmosis system, and point-of-use ultrafilter with or without a softener prior to carbon filtration.
- Bacterial proliferation is a major concern for mobile units.
- Steps to minimize bacterial proliferation include:
  - Use a direct water feed system instead of a storage tank.
  - Place ultrafilter at water source point-of-entry.
  - Use a backflow prevention device in case the mobile system is connected directly to the hospital potable water supply.

Vascular Access Complications

CVC dysfunction

Signs of vascular access dysfunction: progressive reduction in blood flow by more than 10%, reduced clearance, increased pump

pressures (ie, arterial pressure [prepump] more negative than −250 mm Hg or a venous pressure [postpump] >250 mm Hg)

Causes of CVC dysfunction: intraluminal or pericatheter thrombosis, fibrin sheath formation around the CVC, mural thrombus adhering to the CVC tip, or new central venous stenosis

- Early catheter dysfunction is likely due to catheter malpositioning or kinking. KDOQI: "If the CVC is found to be malpositioned within the first week of placement, it should be exchanged for one of proper size/length and properly situated."
- Late catheter dysfunction may be due to intrinsic or extrinsic thrombus or central vein stenosis (particularly with subclavian catheters).
  - Intrinsic thrombus refers to thrombus formed within the catheter (intraluminal thrombus), at the catheter tip (catheter tip thrombus), or outside the catheter as a sleeve or sheath (fibrin-sheath thrombus).
  - Extrinsic thrombus refers to thrombus formation extending outside the catheter into the vascular structure surrounding the catheter.

Management of CVC-related thrombus

- CVC-related central vein thrombosis: systemic anticoagulation for 3 months with or without catheter removal
- CVC-related atrial thrombus:
  - For thrombus less than 2 cm, remove CVC.
  - For thrombus 2 to 6 cm, catheter-directed therapy (CDT) with thrombolytics. If CDT is not available or is unsuccessful, anticoagulation (eg, apixaban) or systemic thrombolysis may be considered if clinically safe. Consult hematology for risks/benefits of the chosen agent.
  - For symptomatic patients with thrombus greater than 6 cm, surgical removal of catheter and thrombus if possible. For asymptomatic patients, CDT may be tried first.

- For mural thrombus (presumably caused by mechanical trauma to the atrial wall from catheter tip), the catheter can be removed as CDT is initiated because the risk of embolization is low. After resolution of thrombus, follow-up imaging should be obtained 7 to 10 days to rule out recurrence.

NOTE

CVC-related atrial thrombus should be considered in HD patients with cardiac problems (eg, tricuspid regurgitation, right HF, cardiac arrest, pulmonary or systemic emboli, or unknown source of infection).

- CVC intraluminal thrombus:
  - "KDOQI considers it reasonable for a conservative bedside approach to managing CVC dysfunction prior to other medical or mechanical interventions (Expert Opinion)," that is, maneuvers to dislodge thrombus:
    - Reposition patient in Trendelenburg position
    - Forceful saline flushes
    - Switch arterial and venous ports to complete HD treatment
  - Specific CDT:
    - Catheter-tip thrombus: Leave the catheter in place to reduce the risk of embolization until the thrombus has resolved, at which time, the catheter may be removed.
    - Intraluminal thrombus: initial trial of forceful saline flushes; if this technique fails, give a trial of intraluminal tissue plasminogen activator (tPA) (alteplase or urokinase plus citrate 4% per limb). KDOQI suggests alteplase 2 mg in preference to 1 mg in each CVC port.
    - Fibrin-sheath thrombus: Attempt to disrupt the fibrin sheath (eg, percutaneous fibrin-sheath stripping, angioplasty disruption, or internal snare maneuver).

NOTE

Recurrent need for intraluminal thrombolytics should raise suspicion for the presence of fibrin sheath.

Prevention of CVC thrombus formation

- Proper flushing and locking of catheter with an appropriate anticoagulant following dialysis
- Routine use of systemic antithrombotic prophylaxis for HD catheters to prevent catheter dysfunction is not recommended.

Vascular access infections (KDOQI 2019, Am J Kidney Dis 2019)

Exit site infection: treat with appropriate antibiotics for 7 to 14 days

Tunnel infection: treat with appropriate antibiotics for 10 to 14 days; catheter removal and reinsertion at noninvolved site

Catheter-related bloodstream infection (CRBSI)

CRBSI is defined as having clinical manifestations (eg, fever or chills, hemodynamic instability, CVC dysfunction, hypothermia, nausea and vomiting, and generalized malaise) plus

- One or more **positive blood culture** from a peripheral source (dialysis circuit or vein) without any other apparent source, plus either:
- **positive semiquantitative** (>15 CFU/ catheter segment, hub or tip) or quantitative (>10^2 CFU/catheter segment, eg, hub or tip) culture,
- by the **same organism** (species and antibiogram)
- If available, the following findings would be supportive of CRBSI:
  - Simultaneous quantitative cultures of blood samples with a ratio of 3:1 or higher (catheter hub/tip vs peripheral [dialysis circuit/vein])
  - Differential period of catheter versus peripheral blood culture positivity of 2 hours

Management of the catheter in CRBSI

Management depends on time frame to resolution of symptoms, blood cultures, organisms, and evidence of exit site infections.

- Duration of antibiotic/antifungal treatment:
  - Coagulase-negative *Staphylococcus* or gram-negative bacilli: 14 days
  - *S. aureus*: 4 weeks
  - Fungemia: 4 to 6 weeks
- Immediate removal of CVC
  - Tunnel infection
  - Infection involving **S. aureus*, *Pseudomonas aeruginosa*, fungal or mycobacterial organisms

  *Of interest, catheter salvage in a significant proportion of patients in the context of *S. aureus* infection has been reported in observational studies.
  - Severe sepsis and/or hemodynamic instability
  - Metastatic infection
  - Persistence of fever or bacteremia 48 to 72 hours after initiation of antibiotics to which the organism is susceptible
- Catheter salvage:
  - Attempt at salvage of the catheter may be attempted for infections involving coagulase-negative *Staphylococcus* or gram-negative organisms if good response to treatment and no fever or bacteremia beyond 48 to 72 hours.
  - Risk of recurrent bacteremia if the catheter is not removed has been shown to be reduced with the use of an antibiotic "lock."
- Removal of CVC with replacement over a guidewire may be attempted if no purulence or other signs of infection at the exit site or tunnel if exchanging over the same site. For tunnel infections, if there is purulence or other signs of infection at the exit site or tunnel, exchange may be possible over a new noninvolved insertion site using the same side to preserve access.

- Evaluation for metastatic infection including echocardiogram to exclude endocarditis should be strongly considered for patients with infections involving *S. aureus* or fungal organisms, or if persistent fever or bacteremia.
- Strategies to reduce CVC infection rate: infection surveillance and feedback, strictly follow proper hand hygiene practices and proper CVC/vascular access care protocols, staff education and competency, patient education and engagement, CVC reduction efforts, chlorohexidine for skin antisepsis, CVC hub disinfection, antimicrobial ointment

Other HD Complications

HTN management in HD patients

- In in-center HD patients, home BP and ambulatory BP measurements better diagnose HTN than dialysis unit measured values.
- Predialysis SBP greater than 160 or less than 130 mm Hg likely has worse survival ("U" curve).
- BP treatment is associated with lower all-cause mortality and CV events and mortality.
- Intradialytic BP variations: Either significant SBP increase or fall observed with HD is associated with higher mortality, regardless of absolute BP level.

Intradialytic HTN

Mechanisms:

- Removal of dialyzable antihypertensive medications with HD
- Activation of renin-angiotensin system and sympathetic nervous system
- Vascular endothelial damage
- Higher dialysate sodium compared with that of plasma with net sodium retention

- Use of cold dialysate (via systemic vasoconstriction)

Advantages of using carvedilol in patients with intradialytic HTN:

- Nondialyzable; helps maintain stable intradialytic blood level
- Shown to improve endothelial function, intradialytic HTN, and ambulatory interdialytic BP
- May improve survival from CV complications

Suggested target BP for HD:

- For HD patients, target interdialytic BP less than 140/90 mm Hg, postdialysis less than 130/80 mm Hg
- Ambulatory BP measurements: daytime less than 135/80, nighttime less than 120/80 mm Hg
- Treatment to target BP must be individualized.
- Target BP for PD patients is suggested to be less than 130/80 mm Hg.

Strategies to achieve BP goal in the HD patient

- Volume control:
  - Dietary sodium restriction less than 2 g/d
  - Educate regarding IDWG. Higher IDWG is associated with increased mortality. Excess sodium intake directly affects IDWG due to increased thirst.
  - Maximize UF (sequentially) as tolerated and/or dialysis time to achieve "dry weight."
  - Dry weight is not just a nonedematous weight, but the weight at which normotension is achieved without or with minimal need for antihypertensive medications.
  - To achieve dry weight as defined, UF may be done sequentially at 1.05 to 1.1 × IDWG rather than within a single treatment to avoid hemodynamic instability and cardiac stress. If BP can be lowered with sequential UF, gradually reduce antihypertensive medications. Avoid UF rate greater than 13 mL/kg/h due to association with higher mortality.

    - Minimize dialysate [Na^+] to minimize thirst, hence IDWG and BP.
    - For techniques that may be used to help optimize UF, see **Appendix A4.6**.
- Increase dialysis frequency
    - Nocturnal or frequent (6 times/wk) dialysis reduces BP, the number of antihypertensive medications, and LV mass.
    - However, frequent dialysis is associated with more access complications and patient burnout.
- Addition of antihypertensive medications:
    - Select from nondialyzable (or low dialyzability) medications:
        - First-line agents: amlodipine, ARB, ACEi (fosinopril, ramipril, benazepril)
        - Others: MRAs, carvedilol, labetalol, hydralazine, α-blockers, clonidine
    - Avoid dialyzable medications: atenolol, metoprolol, and ACEi (enalapril, lisinopril, and perindopril)

Intradialytic hypotension

- Defined as a symptomatic fall in SBP 20 mm Hg or more or mean arterial pressure (MAP) 10 mm Hg or more requiring intervention
- Associated with increased mortality, clotted vascular access, CV events

Risks: age 65 years or above, low baseline BP, clinically significant pericardial effusion or poor cardiac function, iHD, autonomic dysfunction (diabetes, prolonged uremia), malnutrition, severe anemia

Contributing factors: excessive fluid and/or rapid solute removal, GI blood pooling if eating during dialysis, angina equivalent, pericardial effusion, dialysate factors (use of acetate or low calcium concentrations), dialyzer reaction, warm room temperature, air embolism

Management

- Patient-related behavior: dietary sodium and water restriction to prevent high IDWG and the need for high UF, avoidance of eating prior to and during dialysis
- Adjust antihypertensive medications:
  - Hold antihypertensive medications prior to dialysis.
  - Avoid the use of long-acting vasodilators.
- Dialysis procedure: Reassess dry weight, avoid excessive and aggressive UF, consider increasing dialysis time for slower UF rate (<10 mL/kg/h), reduce dialysate temperature to 1 °C less than patient's body temperature, avoid dialysate [Ca^{2+}] less than 2.25 mEq/L and [Mg^{2+}] less than 1.0 mEq/L.
- Avoid sodium modeling or hypertonic saline since sodium infusion results in increased thirst. A vicious cycle of increased volume intake, increased need for intradialytic volume removal, resultant hypotension, subsequent sodium infusion, increased thirst
- Other:
  - Obtain 2D echocardiogram for evaluation of LV function and pericardial effusion.
  - Correct anemia and hypoalbuminemia if applicable.
  - Consider adding midodrine 5 to 10 mg 30 minutes prior to dialysis. Note that midodrine is dialyzable so it should not last postdialysis. Also, be aware that midodrine can cause bradycardia and should be used with great caution in patients receiving negative chronotropic agents.

Headaches, nausea, vomiting

Dialysis disequilibrium is due to rapid solute removal and subsequent cerebral edema.

- Risks: patients with high BUN level who are aggressively dialyzed, younger age, preexisting neurologic disorders or intracranial pathology, first dialysis, hyponatremia, liver disease, use of low sodium dialysate

- Other associated symptoms: blurred vision, altered mental status, muscle twitching, seizures, coma
- Measures to prevent dialysis disequilibrium:
  - Limit first HD session to 2.0 to 2.5 hours.
  - Limit first dialysis blood flow to 200 to 250 mL/min.
  - Consider sodium modeling or high sodium dialysate to offset rapid extracellular osmolality change (each 1 mmol/L of Na offsets effect of 12 mg/dL of BUN).
  - Consider mannitol in patients with BUN levels greater than 100 mg/dL (1 g/kg).
  - Consider continuous kidney replacement therapy (CKRT) in patients at high risk for dialysis disequilibrium syndrome (preexisting intracranial injury, mass, hemorrhage).

Large volume removal

Hypotension

Acute fall in caffeine level during dialysis in those with habitual high caffeine intake

Electrolyte changes: rapid change in serum sodium concentrations, hypoglycemia (particularly in patients with poorly controlled DM)

Fluoride contaminants from water system (headaches, nausea, chest pain, hypotension, neuromuscular symptoms, cardiac arrhythmias)

Others: subdural hematoma, increased intraocular pressure with dialysis (rare), psychological factors

Unlikely contributing factors: dialyzer membrane composition, biocompatibility

Chest pain

Angina

- Underlying CAD
- Management: aspirin, oxygen supplement, nitrates, morphine as indicated if safely tolerated, cardiac evaluation

- If patient is on a β-blocker, make sure it is nondialyzable (carvedilol, labetalol). Atenolol and metoprolol are dialyzable.
- Dialyzer first use syndrome (reaction to dialyzer membrane)

Allergic reaction to medications given during dialysis (eg, IV iron, antibiotics)

Hemolysis (dialysis induced)

- This is a potentially rapid fatal condition if not recognized immediately.
- Hemolysis differential diagnoses:
  - Problems with dialysate (eg, overheating of dialysate, erroneous electrolyte mixing leading to hypotonic dialysate), faulty water treatments with residual contaminants (eg, metal ions [copper, nitrates], disinfectants [hyperchlorite (bleach), formalin], chloramine from municipal water)
  - Problems with blood flow: kinking of dialysis lines, problems with arterial cannulation or flow limiting blood inflow (using high blood flow through a small gauge needle), blood pump malocclusion
  - Problems unrelated to dialysis procedure: autoimmune hemolysis, thrombotic microangiopathy, sickle cell anemia
  - Clinical signs/symptoms suggestive of hemolysis: chest pain, dyspnea, abdominal/back pain, bradycardia if significant hyperkalemia, port-wine appearance of blood in venous line, pink plasma in centrifuged blood specimens
- Management:
  - Stop HD but do not return hemolyzed blood back to patient if hemolysis is related to the dialysis procedure. Monitor patient for hyperkalemia.
  - Perform root cause analysis.

Air embolism

- Rare with current use of air detectors. Air may also be introduced during placement or removal of CVCs.

- Preventive measures: Avoid extremely high dialysis blood flow, tighten arterial luer lock well, prime dialyzer and tubing system, maintain high blood level in venous air catcher.
- Symptoms:
  - Chest pain, dyspnea, syncope
  - Cerebral air embolism may cause blurry vision, altered mental status, seizures, or stroke.
- Management:
  - Stop HD, clamp venous return, provide 100% oxygen, attempt aspiration of air if catheter is still in place.
  - Traditionally, it is recommended that patient be placed in left Trendelenburg position to get air bubbles to float up away from brain and lungs for symptomatic relief and possibly withdrawal of air from the AV access. Benefit of this maneuver versus leaving patient in supine position is being questioned due to negative study in dogs. Supine positioning may facilitate bedside care.

Pulmonary embolism (thrombus migration from vascular access)

Arrhythmias

- Risks likely associated with underlying ischemic or structural heart disease, LVH, mitral valve calcifications
- Rapid change in potassium with dialysis is a concern, but is yet to be a proven risk.
- Low calcium dialysate

Dyspnea

- Prior to dialysis: volume overload, pneumonia, subacute bacterial infections
- Intra- or postdialysis: angina, allergic reaction to dialysis membrane, pericardial effusion, aspiration, pneumonia, bacteremia, reaction to IV drugs given during dialysis (eg, iron)

Intradialytic allergic reactions

- Implicated etiologic agents: dialyzer components, sterilant, disinfectant, heparin, or other medications infused during dialysis
- Type A allergic reaction: rare, anaphylactoid response
  - Mediated by bradykinin and/or histamine, IgE
  - Possible causes: use of ethylene oxide for dialyzer sterilization; IV iron; use of acrylonitrile 69 membranes in patients receiving ACEi (mediated by bradykinin)
  - Onset within 5 to 20 minutes of starting dialysis
  - Major symptoms: urticaria, bronchospasm, laryngeal edema, burning sensation at access site or systemically, angioedema, anaphylactic shock
  - Minor symptoms: reproducible symptoms with dialysis, rhinorrhea or lacrimation, abdominal cramping, itching
  - Management: Stop dialysis and discard blood, supportive therapy with oxygen, antihistamines, epinephrine, and corticosteroid.
- Type B allergic reaction: mild reaction
  - Complement mediated
  - Onset later than type A and occurs within 20 to 40 minutes of starting dialysis.
  - Common symptoms: nausea/vomiting, chest pain, back pain, dyspnea, hypotension
  - Management: supportive care
- Preventive measures against allergic reactions:
  - Prime dialyzer with saline to wash out the sterilant
  - Switch sterilization from ethylene oxide to steam (heat) or γ or β radiation.
  - Use polyacrylonitrile membrane pretreated with polyethyleneimine markedly reduces bradykinin activation and can be used in patients on ACEi.

- Differential diagnosis of intradialytic allergic reactions: hemolysis, air or thromboembolism, dialysis-associated hypotension, hypoxemia

Water-related reactions

Fevers/chills: Consider bacterial or endotoxin contamination, possibly via back filtration at zero net UF pressure.

Thrombocytopenia: likely due to heparin-induced thrombocytopenia and thrombosis (HITT), particularly if seen 4 to 10 days following heparin administration. This condition is due to the production of antibodies that bind to complexes of heparin and platelet factor 4, leading to platelet activation and promotion of a prothrombotic state.

- Symptoms may include HTN, transient global amnesia, profuse diarrhea.
- Thrombocytopenia may occur with E-beam sterilization.

Vascular access (AVF and AVG) dysfunction/complications

Concurrent drop in dialyzer arterial and venous pressures: A simultaneous fall of greater than 25 mm Hg in the arterial and venous pressures suggests a severe postpump kinked tubing.
Access recirculation (ie, uptake of freshly dialyzed blood back into the dialyzer occurs when the dialyzer blood flow is greater than that of access blood flow)

- Causes of access recirculation:
  - Downstream stenosis or thrombosis
  - Arterial stenosis
  - Close needle placement or reversal of lines
- Screening options if clinically indicated:
  - Doppler ultrasound
  - Transonic access blood flow: Flow less than 600 mL/min or reduced by 25% or more from baseline flow suggests increased risk for access recirculation.

- Ultrasound dilution: For interested readers, see Suggested Readings, Depner TA, et al. ASAIO J; 1995.
- Static venous pressure
- Obtain peripheral, arterial, and venous urea concentrations to assess the percentage of recirculation:

$$\% \text{ recirculation} = ([P - A]/[P - V]) \times 100$$

where
P = plasma urea concentration, A = access arterial urea concentration, and V = access venous urea concentration. A value more than 10% warrants investigation for recirculation. A value greater than 25% suggests significant access recirculation.

Vascular access aneurysm/pseudoaneurysm (A/P)

- A pseudoaneurysm is composed of a hematoma and fibrous tissue that may expand with recurrent injury at the same vascular access site.
- An aneurysm may form at the outflow vein/graft of an AV access resulting in progressive dilatation from the high blood flow and vascular damage.
- Vascular access hemorrhage may occur with rupture of a pseudoaneurysm or aneurysm (pseudo/aneurysm).
  - If rupture occurs, apply direct point pressure over area with finger.
  - Rope-ladder technique in cannulation is thought to minimize the risk of A/P formation compared with buttonhole technique.
- KDOQI 2019 "considers" the following regarding A/P:
  - "It is reasonable to proactively educate patients on emergency procedures for aneurysm rupture and to obtain proactive surgical assessment when clinical findings suggest an AV access A/P to be at risk of complications. An A/P that is considered at risk of complications is one with evidence of associated symptoms or skin breakdown."
  - "It is reasonable to obtain emergent surgical assessment and treatment for AV access A/P complications such as erosion or

hemorrhage."

- "It is reasonable to use duplex ultrasound to corroborate the physical examination suggesting an AV access A/P and to obtain information on the size, presence of stenosis/thrombus, and impact on the AV access (including flow rate and status of the arterial inflow and the venous outflow)."
- "It is reasonable to avoid cannulating the access segment(s) that involve the A/P if there are alternative sites. In the rare scenario where there are absolutely no suitable alternative cannulation sites, the sides (base) of the A/P should be cannulated (ie, avoid the top)."
- "It is reasonable to obtain appropriate imaging of the arterial inflow and venous outflow to assess volume flow or stenotic problems that may need correction prior to or during definitive treatment of symptomatic A/P."
- "It is reasonable that surgical management is the preferred treatment for patients with symptomatic, large, or rapidly expanding AV access A/P."
- "It is reasonable that open surgical treatment should be deemed the definitive treatment for AV access A/P."
- "It is reasonable to use covered intraluminal stents (stent grafts) as an alternative to open surgical repair of AV access A/P, only in special circumstances such as specific patient contraindication to surgery or lack of surgical option, due to the associated risk of infection in this scenario."

High-flow AV access

- Increased flow rates through an AV access can lead to high output HF, pulmonary HTN, central venous stenosis, venous HTN, aneurysmal degeneration of the AVF, and hand ischemia.
- AV arterial flow rate (Q_a) greater than 1.0 to 1.5 L/min or Q_a more than 20% of cardiac output (CO) indicates high flow.
- Management:

- Evaluation with 2D echocardiogram to evaluate for changes in cardiac function and Q_a/CO depending on patient's circumstances and local resources is reasonable.
- If significant, consider "flow-reducing therapies" or "banding" of AV access.

AVG seroma

- AVG seromas are fluid collections that form in the early postoperative period around prosthetic AVGs, typically near the anastomotic site.
- Causes: transudation of fluid through the graft material or disruption of surrounding lymphatic system
- Management: typically resolves with observation. If persistent, consider AVG replacement with a different material tunneled through a different anatomic course.

Peritoneal Dialysis (PD)

Solute clearance

PD relies on both diffusion and convection across peritoneal membrane for solute clearance. Water clearance occurs via osmosis and depends on the osmolality of the dialysate.

Indications for PD

- Patients who prefer PD or refuse HD
- Patients who cannot tolerate HD due to poor CV function or who have no vascular access (eg, severe congestive heart disease, extensive vascular disease)
- Patients who prefer home dialysis modality and cannot perform HHD
- No HD availability

Absolute contraindications for PD

- Loss of peritoneal function, UF failure

- Intra-abdominal adhesions blocking dialysate flow
- Surgically uncorrectable abdominal hernia
- Abdominal wall stoma
- Diaphragmatic fluid leak
- Inability to perform exchanges in the absence of a suitable assistant
- Poor hygiene, inability to safely perform PD for any reasons
- Active abdominal inflammatory diseases (eg, diverticulitis, ischemic bowel disease, intra-abdominal abscess)
- Homelessness

Relative contraindications for PD

- Recent abdominal aortic graft
- Large kidneys due to PKD
- Hernias
- Ostomy
- Abdominal adhesions
- Ventriculoperitoneal shunt
- Intolerance of intra-abdominal fluid in patients with morbid obesity
- Severe malnutrition
- Uncontrolled skin infection
- Bowel disease
- *S. aureus* carrier

PD membrane

- Membrane used for the dialysis procedure is the patient's own peritoneal membrane.
- Resistance for solute movement from the circulation across the membrane into the abdominal cavity depends on stagnant capillary fluid film, capillary endothelium, endothelial basement

membrane, interstitium, mesothelium, and stagnant peritoneal membrane fluid film.

- The natural peritoneal membrane has pores of various sizes that allow the bidirectional movement of solutes of different sizes, mostly removal. In general, these pores are classified into three-pore sizes, known as the "three-pore size model":
  - Large pores, 20 to 40 nm, are responsible for solute removal by convection and protein loss.
  - Small pores, 4 to 6 nm, correspond to interendothelial clefts, allow for diffusion of smaller molecules across the membrane, including urea, Cr, Na^+, and K^+. Small pores also allow dextrose to move from peritoneal fluid across the membrane into circulation.
  - Ultrapores, less than 0.8 nm, correspond to aquaporins (AQPs) that are responsible for H_2O removal without concurrent solute/sodium removal, a process known as "H_2O transport sieving" or "sodium sieving" since solutes/sodium are "left behind."

Optimization of PD membrane

- The peritoneal surface area may be increased by using a larger dialysate volume for greater dialysis efficiency. The larger the volume, the larger the contact surface for dialysis. The maximum peritoneal dialysate volume tolerated is typically 2 to 3 L.
- Unlike HD membranes, the intrinsic characteristics of the peritoneal membrane cannot be "changed" to optimize dialysis efficiency:
  - Intrinsic peritoneal membrane resistance
  - Hydraulic conductance (density of small pores and ultrapores, distance of capillaries from mesothelium)
  - Effects of inflammatory and sclerotic states of peritoneal membrane on PD: Increased peritoneal vascularity with inflammation leads to higher solute transport into dialysate,

but reduced UF with prolonged dwell due to more rapid achievement of osmotic equilibrium between blood and dialysate.

Factors that determine PD efficiency

- Peritoneal membrane characteristics
- Patient mobility: Inefficient dialysis in immobilized patient is due to stagnant dialysate.
- Concentration gradient between blood and dialysate
- Dwell time and number of exchanges
- UF, which depends on:
  - Concentration of osmotically active agent in dialysate (eg, glucose, icodextrin)
  - Hydrostatic pressure gradient (patient's BP)
  - Fluid absorption back into the circulation
  - Capillary vasodilatory versus vasoconstrictive state
  - Oncotic pressure gradient, which depends on:
    - Sieving property of solute: The higher the sieving coefficient (how easily the solute can cross the membrane), the greater the convective transport for the solute.
    - Reflection coefficient of osmotic agent in dialysate (high value suggests agent does not cross the membrane easily, but "reflects" back into peritoneal fluid). Maintenance of the osmotic gradient depends on the reflection coefficient for the osmotic agent (ie, glucose: 0.03, polyglucose icodextrin ~1.0). The agent with a high reflection coefficient (icodextrin) can maintain the osmotic difference between the blood and dialysate better, hence better osmotic force favoring UF into the peritoneum.

NOTE

- Icodextrin solution may be considered in patients with DM (or high transporters) who do not achieve adequate UF with dextrose solutions.
- Caution with the use of icodextrin (**Table 4.6**):
  - The metabolites of icodextrin, maltose and polysaccharides, can be read by certain handheld glucose monitoring devices as glucose, thereby falsely reporting high glucose concentration readings. This can lead to erroneous insulin administration for a normoglycemic individual with a falsely high glucose level read or mask life-threatening hypoglycemia. Blood glucose monitoring in patients using icodextrin dialysate must be done with glucose-specific methods (eg, glucose measurement with routine basic metabolic panel) to avoid erroneously elevated glucose levels registered by handheld glucose monitoring devices.
  - Icodextrin can lead to falsely low levels of amylase in patients with pancreatitis.
  - Icodextrin is contraindicated in patients with known allergy to cornstarch or icodextrin, maltose or isomaltose intolerance, glycogen storage disease, and preexisting severe lactic acidosis.
  - Blistering and exfoliative skin eruptions have been reported with the use of icodextrin.

Table 4.6 Icodextrin

Icodextrin (Extraneal)

Basic characteristics

- Icodextrin is a colloid osmotic agent derived from cornstarch. Extraneal solutions contain 7.5% icodextrin which exerts an osmotic pressure of 282-286 mOsm.
- Icodextrin solutions are iso-osmotic—No water movement occurs via aquaporins, thus no Na sieving effect. Ultrafiltration (UF) with icodextrin occurs via convection through small pores.

Advantages

- High reflection coefficient: Better UF than dextrose-containing dialysate
- ↓Glucose-induced lipid abnormalities
- 3-Fold higher "UF efficiency" compared with dextrose solution (ie, lower carbohydrates absorbed per UF volume achieved)

Potential problems

- Icodextrin is not absorbed across the peritoneal membrane (due to size) but is picked up by lymphatics and returned to circulation where it is degraded to **maltose** by serum amylase and converted by maltase to glucose intracellularly. *Glucose monitors that use glucose dehydrogenase with pyrroloquinoline quinone*

Icodextrin (Extraneal)

or the glucose-dye-oxidoreductase–based reagents are contraindicated as they can read maltose as glucose.

- *Hypersensitivity to cornstarch can result in macular papular skin rash in 10% of patients.*
- *Falsely low amylase because amylase is partially used up in the degradation of icodextrin to maltose. Conditions such as pancreatitis may have falsely low amylase but true high lipase levels.*
- *Contraindications: preexisting lactic acidosis (Extraneal contains lactate and may worsen acidosis if lactate cannot be metabolized to bicarbonate), hypersensitivity to cornstarch, glycogen storage disease, intolerance to maltose or isomaltose*

Abbreviation: UF, ultrafiltration.

- Sodium sieving:
  - Early dwell: Dialysate is diluted by ultrafiltrate from H_2O transport across aquaporin 1 (AQP1) without concurrent Na^+ movement across the peritoneal membrane. Hypernatremia is possible in this phase.
  - Longer dwell: Concentration gradient (lower [Na^+] in dialysate compared to that of blood) favors Na^+ loss into dialysate via smaller peritoneal membrane pores.
  - Na^+ loss is minimal with a 4-hour 1.5% dextrose, 2 L dwell, but can be up to 70 mEq with a 4-hour 4.25% dextrose, 2 L dwell.
  - *Isotonic* icodextrin solution does not activate AQPs as *hypertonic* dextrose solutions. Water transport with icodextrin-containing dialysate only occurs along with solute transport through interendothelial cell pores. There is no sodium sieving with icodextrin.

Dialysis adequacy for PD

For patients with residual kidney function (defined as urine volume >100 mL/d)

- Minimal "delivered" dose of total small solute clearance should be a total (PD and kidney) Kt/V_{urea} 1.7/wk or more. See **Appendix A4.7** for conventional indices for urea clearance.

- Total (PD plus residual kidney function) Kt/V_{urea} should be measured within the first month following dialysis initiation and no less than every 4 months thereafter.
- Whenever residual kidney function is added to PD Kt/V_{urea} to achieve goal, a repeat 24-hour urine collection for K_r must be done at least every 2 months.

For patients without residual kidney function (defined as urine volume ≤100 mL/d)

Minimal "delivered" dose of total small solute clearance (PD alone) should achieve a Kt/V_{urea} 1.7/wk or greater. This is measured within the first month following PD initiation and at least every 4 months thereafter.

Kt/Vurea as a measure for dialysis adequacy in PD is being questioned

- PD does not have good small solute clearance (eg, urea clearance), which explains why PD patients have higher BUN and creatinine than HD patients. However, PD clears many other clinically significant uremic toxins that are not captured with Kt/V_{urea}.
- Lack of data to show that Kt/V_{urea} predicts outcome in PD
- Optimal molecule (middle molecule) to assess Kt/V in PD is not defined.
- Current expert opinions suggest a comprehensive evaluation for PD adequacy based on multiple markers rather than just focusing on Kt/V_{urea} (Kt/V_{urea} is only a marker for small molecule clearance). Other markers to consider include preservation of residual kidney function, mineral metabolism (phosphorus) control, β2-microglobulins, and p-cresol.
- Current European guidelines suggest targeting a minimum weekly Kt/V_{urea} 1.7 or more or weekly CrCl of 45 L or more normalized to 1.73 m^2 BSA (including residual kidney function). Supporting evidence is lacking.

Maintaining residual renal function

- Even preservation of 1 mL/min reduces annual mortality by 15% to 25%.
- Use RAAS inhibitors (can also slow deterioration of residual kidney function)
- Avoid contrast dye, NSAIDs, COX-2 inhibitors, and nephrotoxic agents.
- Use of diuretics for volume control has not been shown to accelerate progression of residual kidney function loss.

Prescription for PD

Empirical prescription (see Table 4.7)

Table 4.7 Empirical prescription for chronic peritoneal dialysis

Empirical therapy

- **Automated PD:** Start at 2-3 exchanges of 1.5-2.0 L volume over 6-8 h, gradually increase up to 10 L/d to be exchanged as 4 × 2 L/night and 2 L day-dwell or 5 × 2 L/night as needed.
- **Continuous ambulatory PD:** Start at 2-3 exchanges of 1.5 L/d, gradually increase up to 8 L/d to be exchanged as 4 × 2 L as needed.
- **Empirical therapy × 1 mo**

Special considerations

- If good residual function → Initiate PD at lower dwell volume and/or lower frequency of exchange.
- If higher UF is needed → Increase glucose concentration to 2.5%; if absolutely necessary, consider doing one exchange using dextrose 4.25% or icodextrin.

Assessment of PD adequacy
Determine Kt/*V* in 1 mo
PET in 4-8 wk after PD initiation to determine transporter type
Adjust PD dose as needed to achieve target total Kt/V_{urea} of 1.7 (the United States)

Dose adjustment per Kt/V and PET
Low Kt/*V*: Increase dwell volume, increase dextrose concentration of one or more exchanges, or add one extra exchange (the latter if acceptable to patient).
PET is mostly used in addressing inadequate clearance or UF concerns.
High (rapid) transporters: Use shorter dwell time, more exchanges; consider one extra exchange using icodextrin.
Low transporters: Use higher volume and longer dwell times.
No change in prescription is needed if clearance and UF are already adequate regardless of PET.

Must keep patient's preference and lifestyle in mind when adjusting PD prescription.

Abbreviations: PD, peritoneal dialysis; PET, peritoneal equilibrium testing; UF, ultrafiltration.

PD prescription modification: PD prescription may be modified to achieve dialysis adequacy based on peritoneal equilibrium testing (PET).

Peritoneal equilibrium testing

- PET assesses membrane solute transport characteristics of individual patients by measuring both membrane diffusive and ultrafiltrative capacity. PET is determined by the molecular weight of the solute of interest, membrane permeability, and effective surface area.
- PET protocol (see **Appendix A4.8**)
- Interpretation of PET (**Table 4.8**):

Table 4.8 Interpretation of peritoneal equilibrium testing (PET)

P/D creatinine	D/D_0 glucose	Transporter type	Comments

0.34-0.50	>0.49	Low	• Slow transporters may be inadequately dialyzed due to low solute removal.
			• Possible PD prescription modifications to increase Kt/V_{urea}:
			  • Increase volume and dwell duration
			  • HD switch if all else fails

>0.65-0.81	>0.26-0.38	High average	• Adjust per lifestyle • May need shorter day dwell if APD
>0.81	0.12-0.26	High (rapid)	• High transporters may be predisposed to malnutrition from increased amino acid losses in the dialysate and decreased fluid removal due to the rapid dissipation of the glucose concentration

P/D creatinine	D/D_0 glucose	Transporter type	Comments

			difference between plasma and dialysate.
			• Possible PD prescription modifications to increase Kt/V_{urea}:
			  • More frequent exchanges, shorter dwell
			  • May need icodextrin-containing dialysate to improve ultrafiltration
			  • HD switch if all else fails

P/D creatinine and D/D_0 glucose ratios as measured after 4 hours dwell of 2 L of 4.25% dextrose.

Abbreviations: APD, automated peritoneal dialysis; D, dialysate concentration; D, dialysate concentration at 4 hours; D_0, dialysate concentration at start of test, which is essentially the dextrose concentration in 4.25% dextrose solution; HD, hemodialysis; Kt/V_{urea}, measure of urea clearance; P, plasma concentration; PD, peritoneal dialysis; UF, ultrafiltration.

- Patients may be categorized as high, high average, low average, to low transporters based on the ratio of dialysate to plasma creatinine (D/P Cr) at 4 hours following a 2-L 4.25% dextrose dwell. Similarly, patients may also be categorized as high, high average, low average, and low transporters based on the ratio of dialysate glucose at 4 hours and dialysate glucose at start of PET testing (D/D_0 glucose).
- A difference in one category between D/D_0 glucose and D/P Cr is acceptable.
- A difference in two categories is NOT acceptable.

- Causes for discrepancy of PET interpretation:
  - Serum glucose greater than 235 mg/dL
  - Data collection or entry error
  - In the case of unexplained discrepancy, rely on D/P Cr

High transporters

- High transporters have more rapid absorption of glucose and dissipation of the osmotic gradient, which results in low UF with

long dwells.

- Prescription considerations: More frequent, shorter duration dwells would optimize solute clearance and UF. If despite doing more frequent exchanges and goal Kt/*V* and UF are not achieved, HD switch may be necessary.

Low transporters

- Low transporters diffuse solute more slowly across the peritoneal membrane and require longer dwells to reach significant equilibrium. UF will be sustained as glucose osmotic gradient is maintained for a longer period of time. However, solute clearance will be slow.
- Prescription considerations: Higher volume and longer dwells would optimize solute clearance.

Average transporters

- Adjust PD prescription to best suit lifestyle.
- Average transporters using automated PD and a long-day dwell may have problem with net resorption with the long-day dwell, in which case, the day dwell may be shortened or performed with icodextrin.

> **NOTE**
>
> In general, although PET guides PD prescription, clinicians should consider a prescription that would best fit patient's lifestyle preference.

PD dialysate

Components of PD dialysate: water, osmotic agent, buffering, electrolytes, and minerals

Osmotic agents

- Commonly used osmotic agents include dextrose (most commonly used), icodextrin, amino acids
- Dextrose-based PD solutions are mixed as 1.5%, 2.5%, and 4.25%, with dextrose concentration equivalent of 1,500, 2,500, and 4,250 mg/dL, respectively. Note that these dextrose

concentrations are much greater than that of plasma (ie, compared with glucose concentration of 100 mg/dL in euglycemic individuals). The great concentration difference acts as to "pull water" from plasma into the peritoneum as UF. In patients with poorly controlled diabetes, UF is reduced due to the loss of this large concentration difference between dialysate and plasma.

- The higher the concentration of the osmotic agent, the greater the UF.
- Agents with low absorbability (ie, icodextrin) retain their UF capacity better with long dwells. See previous important notes on icodextrin.
- The addition of amino acids may be done to improve nutritional status in PD patients.

Buffers

- Buffers are used to correct the metabolic acidosis of ESKD.
- Agents include acetate, bicarbonate, and lactate.
- Most commonly used agent is lactate at concentrations of 35 to 40 mmol/L. Acetate-based solutions are irritating to the peritoneum and can cause pain and sclerosing peritonitis. Bicarbonate can precipitate calcium and magnesium in solution and is not premixed in dialysate bags. However, they can be mixed into the dialysate bag immediately before use.

Electrolytes

- Electrolytes including sodium and calcium are typically premixed in commercial PD dialysates.
- Sodium is premixed at a range concentration of 130 to 137 mmol/L.
- Potassium: K^+ is generally not premixed in commercial PD dialysate. With a zero K^+ solution, serum K^+ concentration can be typically maintained at 4 mmol/L (=4 mEq/L). For patients with hypokalemia, oral potassium supplement may be given or potassium may be added to dialysate bag at a maximum of 4 mEq/L of dialysate to avoid hyperkalemia.

- Calcium: Calcium is typically premixed at 2.5 to 3.5 mEq/L (=1.25-1.75 mmol/L). Similar to HD, the use of lower calcium dialysate in PD can be associated with hypotension.
- Magnesium: Mg^{2+} is premixed in the concentration range of 0.5 to 1.5 mEq/L. A lower range is generally preferred because similar to potassium, magnesium can be easily replaced. If patients cannot tolerate oral magnesium supplement (eg, diarrhea), a higher dialysate Mg^{2+} concentration can be used.

See **Table 4.9** for varying electrolyte concentrations in commonly used PD dialysates.

Table 4.9 Content of peritoneal dialysate solutions

Dialysate content	Dextrose	Icodextrin Extraneal	Amino acids Nutrineal PD4
Concentration of osmotic agent (%)	1.25, 2.5, or 4.25	7.5	1.1
Sodium (mEq/L)	132	132	132
Potassium (mEq/L)	0-2	0	0
Chloride (mEq/L)	96-102	96	98
Calcium (mEq/L)	2.5-3.5	3.5	2.5
Magnesium (mEq/L)	0.1-1.5	0.5	0.5
L-Lactate (mEq/L)	35-40	40	40
Osmolality (mOsm/kg)	346-485	282-286	365
pH	5.2	5-6	5.7-6.8
Major indication	Routine	Improve UF and solute clearance in high average to high transporters	Protein malnutrition

Abbreviations: PD, peritoneal dialysis; PET, peritoneal equilibrium testing; UF, ultrafiltration.

PD catheters

Placement of PD catheter should be done at least 2 weeks prior to PD initiation unless urgent start is necessary.

Antibiotic prophylaxis is recommended for the following:

- Initial catheter insertion: Preoperative use of prophylactic antibiotic (eg, 1 g IV vancomycin) has been shown to reduce postoperative peritonitis compared to cefazolin and control.
- Prior to invasive procedure (eg, dental, colonoscopy, hysteroscopy, cholecystectomy)

> **NOTE**
>
> Patient should report to colonoscopy without PD fluid (or ≤200 mL) in the peritoneal cavity because dextrose provides an ideal culture medium.

PD access issues

- May be done surgically via laparoscopic approach or with interventional radiology under fluoroscopic guidance
- Surgically placed catheter should have folding of omentum to avoid catheter-tip migration and malfunction.
- A surgically inserted catheter with a straight intraperitoneal (IP) segment has been shown to improve catheter survival, not the number of cuffs or configuration of subcutaneous segment.

Special PD issues

Notes regarding PD and morbidity and mortality

- Both lower (<3.5 mEq/L) and higher (>5.5 mEq/L) serum potassium concentration ranges are associated with higher risk for all-cause mortality.
- Unplanned PD (acute PD initiation) does not appear to increase infectious complications compared with planned PD.
- Mortality data regarding the use of PD versus HD for AKI are conflicting. Nonetheless, it must be noted that PD may be the

only available option in developing countries.

- Similar to HD, infection is a common complication. PD-related peritonitis may contribute up to 15% of deaths in PD.

Risks for early switch to HD (ie, by 6 months on PD)

- HD initiation prior to PD
- Development of peritonitis within 6 months on PD
- PD following a failed kidney transplant
- Poor PD expertise by dialysis staff

PD BP and volume control

- BP in PD tends to improve in the first 2 years but subsequently worsens.
- Similar to HD, BP control in PD may be achieved with salt restriction and optimal fluid removal via UF. Diuretic should be added if there is residual kidney function.
- Inadequate UF is a predictor of worse survival.
- Excessive salt restriction and UF, however, are associated with reduced urine volume, possibly loss of residual kidney function, and ultimately reduced survival. The CANUSA study revealed reduction of relative mortality risk to 0.64 for every 250 mL of daily urine output and 0.88 for every 5 L/wk of residual renal GFR.
- RAAS inhibitors should be considered first-line antihypertensive therapy:
  - Have been shown to preserve residual kidney function
  - Have been shown to preserve peritoneal membrane function, evidenced by slower conversion to rapid transporters. Protective effect is presumed to be via antifibrotic properties of RAAS inhibition.
  - Known to be cardioprotective

PD complications

Exit site infections

- Typical organisms: *S. epidermidis* or *S. aureus* > gram-negative organisms (eg, *P. aeruginosa*)
- *Seasonal variations in causative pathogens: S. epidermidis* and gram-negative species in warmer seasons; *Corynebacterium* and fungal species in cold seasons.
- Prophylaxis: Use daily topical mupirocin or gentamicin cream. Polysporin cream may be associated with increased fungal infections.
- Check nasal culture for *S. aureus* carriers and use mupirocin ointment for 7 days monthly for prophylaxis against exit site infection.

Tunnel infections may be diagnosed with ultrasound (or CT) for evidence of fluid collection along the catheter tunnel.

Peritonitis

- Risks:
  - Exit site or tunnel infection
  - Dialysate contamination
  - Leaking from catheter exit site with fluid flowing back into the catheter tract
  - Warmer months (presumably due to increased sweating, moisture in warmer months)
  - Low dialysate [Ca^{2+}] less than 1.75 mEq/L
  - Hypokalemia: thought to reduce intestinal motility and bacterial overgrowth
- Prophylactic measures:
  - Patient education for proper PD techniques
  - Routine use of topical exit site antibiotic creams (mupirocin or gentamicin)
  - "Flush before fill" should be performed for manual PD exchanges to minimize infections.
  - Correction of electrolyte abnormalities, particularly hypokalemia, hypocalcemia, constipation

- Diagnosis of peritonitis:

Must meet at least two out of three criteria:

- Clinical signs consistent with peritonitis such as abdominal pain and/or cloudy effluent
- PD cell count with greater than 100 WBCs/µL or with more than 50% polymorphonuclear (PMN) leukocytes in differential count (>50% PMN is likely a better indicator for peritonitis than having greater than 100 WBC/µL). False negatives may be seen if cell count is obtained early in the course of peritonitis or during short dwell (collect fluid after at least 2-hour dwell time).
- Identification of infective organism(s) from the dialysis effluent via Gram stain or culture
- Note that 15% to 40% of PD fluid cultures are negative in clinical peritonitis. Negative cultures may be caused by recent antibiotic exposure, suboptimal sample collection or culture method, or infection with an atypical organism (such as fungi, *Mycobacterium*, *Campylobacter*, *Ureaplasma* sp., *Mycoplasma*, or enteroviruses).
- Pathogenic organisms:
  - Most common organism: gram-positive cocci (eg, *S. epidermidis*), culture negative, gram-negative organisms, polymicrobials, much less commonly, fungi (*Candida* is most common), and, rarely, TB
  - Streptococcal peritonitis can be associated with severe abdominal pain.
  - If gram-negative organisms (eg, *Escherichia coli* or *Enterobacter*) or polymicrobials, consider bowel perforation or diverticulitis. Diarrhea and constipation are frequent causes for gram-negative organism peritonitis.
  - Risks for fungal infections: immunosuppressive state, DM, malnutrition, recurrent use of multiple antibiotics
- Antibiotic administration:
  - IP route is generally preferred to IV route.

- Empirical therapy per International Society for Peritoneal Dialysis (ISPD): vancomycin or first-generation cephalosporins *plus* third-generation cephalosporin or gentamicin (choice may be based on local organism susceptibility)
- Duration of treatment is generally 2 weeks for *S. epidermidis* and *streptococcal peritonitis* and 3 weeks for *S. aureus* and *corynebacterial peritonitis, and at least 3 weeks for nonpseudomonal gram-negative peritonitis*. A short course of oral rifampicin to eradicate carrier state and adherent or intracellular organisms should also be considered for *S. aureus* peritonitis.
- Enterococcal peritonitis: IP vancomycin for 3 weeks with IP aminoglycoside added for severe cases
- Pseudomonal peritonitis: two antibiotics (eg, IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks
- Polymicrobial peritonitis:
  - Double empirical coverage as above plus metronidazole for at least 3 weeks
  - Evaluate for abdominal pathology/bowel perforation and promptly obtain surgical evaluation.
- The fear for gentamicin-induced loss of residual kidney function (with use up to three courses) is likely unwarranted based on data from ANZDATA registry. However, IP aminoglycoside for over 3 weeks should be avoided due to high ototoxicity risk.

- Antifungal administration:
  - IP antifungal agent has no preferential role over systemic therapy.
  - Aspergillus and non-albicans *Candida* species: Consider echinocandins (eg, caspofungin).
  - Filamentous fungi: Consider second-generation azoles (eg, posaconazole, voriconazole).

- For culture-negative peritonitis not responding to empirical antibiotic or monocytic/eosinophilic peritonitis:
  - Resend PD fluid for special culture techniques.
  - Consider other causes: fungi, virus, mycobacterium, allergic response to peritoneal dialysate (eg, icodextrin) or drugs (look for systemic signs/symptoms of allergic reactions), underlying malignancies, lymphoproliferative diseases, CO_2 infusion with laparoscopic procedures.

Definitions of relapsing, recurrent, repeat, and refractory peritonitis

- Relapsing: same organism within 4 weeks of treatment completion. Likely due to biofilm. Retreat and try tPA (eg, alteplase instillation) (1-6 hours) to remove biofilm. Catheter replacement would be indicated if peritonitis persists or relapses after tPA cleared the infection.
- Recurrent: different organisms within 4 weeks of treatment completion
- Repeat: same organism after 4 weeks of treatment completion
- Refractory: persistent infection after 5 days of appropriate antibiotics

UF failure

- Non-PD procedure–related causes: loss of residual kidney function, congestive HF, dietary noncompliance, PD nonadherence
- PD procedure–related causes:
  - Mechanical problems with PD procedure (migration, kinking of catheter), constipation affecting dialysate flow, fibrin plug (fibrin may be seen in drainage bags). In the case of fibrin plugs, irrigate tubing system and add heparin to dialysate bags.
  - Dialysate leaks to other body cavities
  - Peritoneal membrane failure (see next section)
  - Poorly controlled diabetes (eg, blood glucose >250 mg/dL dissipates the osmotic gradient necessary for optimal UF)

- Increased lymphatic reabsorption associated with increased intra-abdominal pressure: Sitting position is worse than standing and lying positions.
- Intra-abdominal pathology

Peritoneal membrane failure

- Peritoneal membrane failure may be diagnosed as follows:
  - Inability to maintain euvolemia despite use of more than three hypertonic dialysate solutions per day, or
  - Failure to ultrafilter greater than 400 mL with a 4.25% solution over 4 hours (Rule of 4s), or
  - PET revealing high D/P of creatinine (ie, >0.8)
- Causes of peritoneal membrane failure:
  - Early: acute inflammation
  - Late: alterations in peritoneal membrane (eg, thickening, fibrosis)
- Management of high transporters:
  - Strict dietary salt and water restriction
  - Use high-dose diuretics if residual kidney function (consider bumetanide over furosemide for better bioavailability and less ototoxicity).
  - Replace one or two 1.5% exchanges with a more hypertonic dialysate (2.5% or even 4.25% dextrose); consider one exchange with icodextrin daily.
  - Shorten dwell times; consider switching from continuous ambulatory peritoneal dialysis (CAPD) to nighttime automated PD with or without mid-day exchange depending on residual kidney function.
  - Switch to HD if all else fails.

Peritoneal fibrosis

Suggested fibrosis-inducing factors: TGF-β, atrial natriuretic peptide, aldosterone

Encapsulating peritoneal sclerosis (EPS)

- Severe form of peritoneal sclerosis, manifested as abdominal pain, thickened bowel walls, bowel obstruction, with possible associated weight loss
- Risk factors: severe peritonitis, discontinuation of PD, genetic predisposition, PD vintage, younger age, high glucose load and chronic exposure to glucose degradation products
- Clinical manifestations:
  - Abdominal pain, bowel obstruction, UF failure, malnutrition, weight loss, bloody dialysate
- Diagnosis:
  - The diagnosis of EPS requires the presence of both clinical and radiologic features of intestinal obstruction and encapsulation.
  - CT findings of thickening of peritoneal membrane or encapsulation of bowel loops, bowel tethering, peritoneal calcifications
- Management:
  - Early dietetic referral
  - Medical therapy:
    - Reported therapies that may be considered at the discretion of the treating clinician: tamoxifen (inhibitor of TGF-β production), immunosuppressive therapy (eg, prednisone, azathioprine, mycophenolate mofetil)
    - Experimental interventions: *N*-acetylcysteine, eplerenone, glutamine supplementation, and the vasoactive glycosaminoglycan sulodexide
    - Surgical intervention by experienced EPS surgical team
    - Peritoneal rest, transfer to HD (per patient wishes, life expectancy, quality of life), consider total parenteral nutrition.

Dialysate leaks (subcutaneous or other body cavities)

- Early leaks (usually external leak):

    - Poor tissue healing due to early use of PD following catheter insertion
    - Faulty catheter implantation, trauma
    - Diagnosis: Check glucose concentration with Chemstrip to confirm pericatheter leaks. This should reflect the glucose concentration from the dialysate.
    - Management: Provide prophylactic antibiotic to prevent peritonitis and hold PD for 1 to 3 weeks.
- Late leaks: hernias, straining, infections
    - Obtain T2-weighted MRI (dialysate can be detected without the use of Gd), CT with addition of contrast to dialysate, or nuclear study with addition of tracer to dialysate. CT and nuclear study only detect current leaks, whereas MRI can detect existing leaks.
    - Perform physical examination to assess for obvious fluid collections.
    - If icodextrin dialysate is used, addition of povidone iodine to the aspirated fluid will turn bluish black. This is due to the reaction between iodine and icodextrin starch.

Infusion pain

- Underlying etiologies:
    - Usually transient and observed in new patients
    - Persistent infusion pain:
        - Low dialysate pH
        - Hypertonic glucose solutions
        - Aged dialysis solution
        - Overdistention of the abdomen with high dialysate volume
        - Extremes in dialysate temperature
        - Catheter related: Catheter malposition with tip against abdominal wall or tube restriction by attached tissues can produce both inflow and outflow pain. Straight-tip catheters

have higher incidence of mechanical inflow pain compared with coiled catheters.

- Diagnosis: Consider all above—clinical judgment.
- Interventions:
  - Use bicarbonate/lactate-buffered dialysis solutions (pH 7.0-7.4).
  - Consider adding 1% to 2% lidocaine solution to dialysate (5 mL/L).
  - Other considerations: Use slow infusion rate, lower volume, adjust dialysate temperature; consider imaging study (CT).

Drain pain

- Underlying etiologies:
  - End-of-drain pain: typically occurs at the end of drain as catheter touches sensitive parietal peritoneum; pain is typically experienced in the genital or anorectal region and more commonly occurs with the use of cycler.
  - Low catheter implant: Catheters implanted too low on abdominal wall can wedge tubing into deep pelvis, resulting in drain pain.
  - Constipation: crowding of bowels around catheter
- Diagnosis: clinical judgment—rule out conditions above
- Interventions:
  - Avoid complete drain
  - Consider tidal PD (fill following incomplete drain)
  - Treat constipation if applicable
  - Consider repositioning of catheter

Outflow failure

Possible etiologies of outflow failure include:

- Constipation and urinary retention: Compression on catheter may block catheter side holes or displace catheter tip into a position of poor drainage.
  - Urinary retention: Drain bladder as needed.

    - Constipation: Administer oral emollient, stool softeners. Note that stimulants such as bisacodyl and saline enemas are reserved for refractory cases due to possible chemical and mechanical irritation of colonic mucosa and potential transmural migration of bacteria and development of peritonitis.
- Tubing kink: typically results in two-way obstruction; diagnosis: abdominal x-ray; treatment: catheter revision or replacement
- Fibrin strands and plugs: diagnosis: Fibrin strands and plugs may be seen in effluent; treatment: Add heparin 500 units/L of dialysate.
- Obstructed catheter:
    - Attempt dislodging intraluminal debris by brisk irrigation of catheter with saline. If this fails, consider trial of plasminogen activator (tPA) instillation.
    - If tPA still fails, consult interventional radiology or general surgery for catheter manipulation.

Shoulder pain (other than anginal causes)

- May be caused by unintentional air infusion during dialysate solution instillation
- Management: Infuse full exchange volume, then drain dialysate with patient in knee-chest position.

Respiratory distress

- May be due to excessively high volume of dialysate in the peritoneal cavity

Bloody dialysate

- Etiologies to consider: menstruation, ruptured ovarian cysts, ruptured capillary, bowel ischemia/infarction, intra-abdominal malignancy, trauma, early EPS, mycobacterium
- Performing an exchange with room temperature PD fluid may clear bloody dialysate. Add heparin to dialysate to avoid clotting of catheter if benign cause.

Green dialysate: Consider biliary source.

Milky white dialysate: hyperlipidemia (TGs or chylomicrons), disruption of lymphatics

Indications for PD catheter removal

- Refractory tunnel infection or severe exit site infection
- Refractory peritonitis (treatment failure despite appropriate antibiotics >5 days)
- Catheter-related sepsis
- Fungal peritonitis
- Abdominal perforation
- Presence of biofilm in patients with relapsing peritonitis that failed tPA administration to clear the biofilm

Consider PD catheter removal

- Recurrent peritonitis
- Mycobacterial peritonitis
- Peritonitis caused by multiple enteric organisms

Catheter reinsertion

- Systemic antibiotics should be continued for at least 2 weeks prior to reinsertion.
- Reinsertion may be done at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms.

SPECIAL TOPICS IN CKD

Dermatologic Issues in ESKD

Nonspecific manifestations

Pallor (40%): likely due to anemia
Hyperpigmentation (20%): thought to be due to increased concentrations of melanocyte-stimulating hormone. Treatment: sunscreen

Half-and-half nails (a.k.a. Lindsay nails) (20%): Proximal half of nail is white, distal half of nail is normal or brown in color. Thought to be due to increased tissue concentration of melanocyte-stimulating hormone. Benign, no treatment

Xerosis, dry scaly skin (50%-85%): thought to be due to dehydration of stratum corneum and reduced sebum and sweat production. Treatment: routine skin emollient application, avoid excessive washing

Uremic pruritis

- Likely multifactorial, suggested contributing factors: hypervitaminosis A, secondary hPTH, high levels of calcium, phosphorus, magnesium, iron deficiency anemia, xerosis, increased inflammatory cytokines, abnormal neurologic signaling, imbalance of endogenous CNS opioid peptides, downregulation of κ-opioid receptors
- Management: dialysis optimization, skin moisturization and emollient application, itch-specific therapy (FDA-approved κ-receptor agonist difelikefalin infusion after each dialysis therapy, off-label use of gabapentin [100 mg daily] or pregabalin [25 mg daily]), second-line itch-specific therapies (ultraviolet B phototherapy and selective serotonin reuptake inhibitors)

Acquired perforating dermatosis (up to 10%)

- Unclear etiology, mostly affect African Americans, strongly associated with CKD and DM, characterized by transepidermal absence of dermal structures (ie, collagen, keratin, elastic fibers)
- Clinically manifested as localized pruritus, presence of firm, dome-shaped papules or nodules with central keratotic plugs on extensor surfaces of extremities and trunk. New lesions with trauma/scratching may form (Koebnerization).
- Treatment options:
  - Topicals: steroid creams (clobetasol or β-methasone) and/or a keratolytic agent (salicylic acid, urea, or ammonium lactate); retinoid; cantharidin

- Oral therapies: antihistamines, low-dose allopurinol, acitretin, doxycycline or minocycline
- Others: cryotherapy, phototherapy

Bullous diseases

Porphyria cutanea tarda (PCT) is due to uroporphyrinogen-decarboxylase (URO-D) deficiency and is exaggerated by alcohol abuse, hepatitis C, HIV, and iron supplementation. HD patients may develop PCT due to decreased URO-D activity and poor clearance of plasma porphyrins. PD patients are less susceptible to PCT due to better porphyrin clearance. Management: avoidance of triggers (eg, alcohol, hepatotoxic medications, sun exposure, iron overload) and use of high-flux dialyzers for effective porphyrin removal.

Pseudoporphyria is clinically and histologically similar to PCT, but without serum and urine porphyrin abnormalities. Management: avoidance of triggers (eg, diuretics, antibiotics, antifungals) and sun exposure. Consider *N*-acetylcysteine.

Calcific uremic arteriolopathy (calciphylaxis)

- Condition characterized by calcification, microthrombosis, and fibrointimal hyperplasia of subcutaneous and dermal arteries and arterioles, cutaneous ischemia, and septal panniculitis
- Associated with high morbidity and mortality (up to 45%-80% mortality within 1 year)
- Diagnosis may require a high index of suspicion in the appropriate clinical setting. Clinical manifestations may mimic other conditions such as cellulitis, vasculitis, or complications of large vessel peripheral vascular disease. Skin biopsy findings may be suggestive but are not diagnostic. Plain x-rays of the involved extremity showing calcification of small vessels may be suggestive of the diagnosis.

Clinical manifestations: severely painful nodules, plaques, or ulcers, livedo reticularis. Skin surrounding lesion has been described as having a leather-like texture. Pain may precede the appearance of

skin lesions. Often, lesions are on proximal extremities and the trunk as opposed to distal extremities that might be due to large vessel vascular disease.

Pathogenesis: unclear but thought to be due to an imbalance in vascular micro-milieu between procalcifying factors (eg, osteocalcin, osteonectin, alkaline phosphatase, collagen I) and anticalcifying factors (eg, matrix G1a protein, fetuin, pyrophosphate, osteoprotegerin), leading to the deposition of carbonated apatite in vasculature

Risk factors

- Patient-related factors: female gender, obesity, rapid weight loss, genetic predisposition
- Medical history–related risks: dialysis vintage, autoimmune disease, T2D, recurrent hypotension, hepatobiliary disease, metastatic cancers, primary or secondary hPTH, thrombophilia (eg, antithrombin deficiency, protein C deficiency, lupus anticoagulant), skin trauma (eg, repeated insulin injections), ABD, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)
- Laboratory abnormality-related risks: hypoalbuminemia, hypercalcemia, hyperphosphatemia
- Exposures and medication-related risks: ultraviolet light, aluminum, steroids, warfarin, subcutaneous insulin, vitamin D analogs, calcium-based phosphate binders, iron therapy, recombinant PTH (teriparatide)

Potential therapy

- Avoid: warfarin, vitamin D analogs, calcium-based phosphate binders
- Supportive care: wound care (which may include treatment with hyperbaric oxygen), control of secondary hPTH and hyperphosphatemia, use lower calcium dialysate (only if safely tolerated due to hypotension associated with lower calcium dialysate), debridement only when absolutely necessary due to an

increased risk of infections, consider bisphosphonate therapy and cinacalcet if clinically appropriate

- IV sodium thiosulfate 25 g thrice weekly can be administered during the last 30 minutes of each HD session. Efficacy is variable and duration of therapy is undefined, but most reported cases required prolonged treatment of weeks to months. Side effects of sodium thiosulfate include nausea, elevated anion gap metabolic acidosis (due to accumulation of lactic acidosis, thiosulfuric acid, and hydrogen sulfide), volume overload, QTc prolongation, and hypocalcemia.
- Optimize dialysis dose in dialysis-dependent individuals.
- Promising therapy under clinical investigation: SNF472 is an IV formulation of myoinositol hexaphosphate that can directly inhibit the formation of calcium and phosphorus crystals, thereby preventing ectopic calcium deposition.

Dialysis β2-microglobulin amyloidosis

β2-Microglobulin is a major constituent of amyloid fibrils that can deposit in synovial membranes and osteoarticular sites, leading to destructive osteoarthropathies or major solid organs such as heart and GI tract.

Incidence more than 95% with greater than 15 years of HD vintage in the past, but likely lower at present due to greater removal of β2-microglobulin with high-flux dialysis

Increased risk: long-term HD or CAPD

Clinical manifestations: carpal tunnel syndrome, flexor tenosynovitis, subchondral bone cysts/erosions, fractures, HF, pulmonary HTN, GI bleed

Pathogenesis: poor clearance without residual kidney function, inflammatory state, prolonged uremic exposure, advanced glycation end products of β2-microglobulin

Management: supportive, physical and/or occupational therapy, surgical repair

CKD in Special Clinical Settings

Nephrosclerosis with aging

Structural changes with aging

- Reduction in kidney mass: 250 to 270 g kidney mass in 40 to 50 years old becomes 180 to 200 g by the age of 70 to 90.
- Cortical thinning with relative medullary sparing (likely due to increased glomerulosclerosis)

Histologic changes with aging

- Focal global glomerulosclerosis, thickening of glomerular basement membrane, mesangial expansion, ischemic changes with segmental adhesion to Bowman capsule
- Tubular atrophy with cystic formation, interstitial fibrosis
- Arteriolar intimal fibrosis—may be associated with thinning of media; hyaline arteriosclerosis seen in smaller vessels

Functional changes with aging

- GFR reduction of 0.8 mL/min/1.73 m^2/y after age 40 may be observed.
- GFR decline of 7 to 8 mL/min/1.73 m^2/y in those with underlying CKD
- Albuminuria in 30% among patients aged 70 years or above
- Reduced concentrating and diluting capacities, which explains the propensity for increased nocturia and hyponatremia, respectively, in the older patients
- Normal renal reserve

CKD and pregnancy

Effects of pregnancy on volume homeostasis and the kidneys in women with *normal* kidney function:

Volume and electrolytes

- Total Na^+ retention 950 mmol = 22 g
- Total water retention 6 to 8 L

- Plasma volume increases by 30% to 45% (up to 1.25 L) by the second trimester.
- Lower serum osmolality of 270 to 275 mOsm/kg versus nonpregnancy range of 280 to 290 mOsm/kg
- Lower S[Na^+] of 132 to 135 versus nonpregnancy range of 138 to 142 mmol/L
- Lower serum osmolality and hyponatremia may be due to increased antidiuretic hormone (ADH) due to systemic vasodilation or "underfill," or due to reset osmostat, which may be mediated by β-human chorionic gonadotropin (β-hCG).

Kidney function

- Renal plasma flow and GFR increase by 50% by the second trimester, and kidney size increases by 1 cm in length. Hemodynamic changes during pregnancy are essential for normal fetal growth and development. Reduced renal function can adversely affect fetal outcomes.
- Glomerular hyperfiltration causes the midterm SCr to be as low as 0.4 to 0.6 mg/dL. An SCr 1.0 mg/dL or more is most likely abnormal. Glomerular hyperfiltration in pregnancy accelerates CKD progression.
- Increased loss of water-soluble vitamins, hence the need for prenatal vitamins
- Increased proteinuria related to hyperfiltration up to 300 mg/d or uPCR up to 0.3 g/g creatinine is normal (predominantly tubular [LMW, nonalbumin] proteinuria).
- Glucosuria is considered physiologic for later stages of pregnancy, which may be due to reduced tubular reabsorption or hyperfiltration overflow. However, early glucosuria requires testing for glucose intolerance or undiagnosed DM.

Hemodynamic changes

- Reduced vascular resistance:
  - Systemic arterial vasodilation mediated by NO and relaxin
  - Relative resistance to vasoconstrictors such as Ang II

    - ADH and RAAS are increased to counteract changes above, but the net effect is still reduction in vascular resistance.
- Increased CO, increased thirst
- Decreased systemic BP:
    - Diastolic BP decreases by 7 to 10 mm Hg in early pregnancy, by as much as 20 mm Hg in mid-pregnancy, and returns to baseline by the third trimester.
    - SBP only decreases slightly due to increased CO (which offsets the reduction in peripheral resistance).

Baseline creatinine in pregnant patients with CKD predicts poor outcomes

- Baseline creatinine less than 1.5 mg/dL:
    - Permanent loss of GFR in less than 10% of women
    - Live births in more than 90% of women
- Baseline creatinine 1.5 to 2.5 mg/dL:
    - Maternal HTN and proteinuria in 50%
    - Decline or permanent loss of GFR in 30% of women
    - 10% incidence of ESKD soon after pregnancy
    - 60% risk of preterm delivery, 37% intrauterine growth retardation, and 7% fetal loss
- Baseline creatinine greater than 2.5 mg/dL:
    - Progression to ESKD highly likely during or soon after pregnancy
    - High rate of fetal loss

> **NOTE**
>
> Poorly controlled HTN exaggerates kidney injury and GFR decline in pregnancy.

Management of patients with CKD during pregnancy

- Discontinue ACEi/ARB and statin (and/or other medications contraindicated during pregnancy due to the risk of fetal

abnormalities).

- Immunosuppressive therapy: If patient is on immunosuppressive therapy, see **Chapter 8: Transplant Immunobiology**.
- Monitor creatinine and proteinuria (uPCR).
- BP control: see **Chapter 5: Hypertension**
- Consult high-risk obstetrics for co-management.
- Reduce preeclampsia risk:
  - Initiate low-dose aspirin (eg, 81 mg/d) prior to 16 weeks of gestational age, and continue until delivery for women with high risk for preeclampsia. High preeclampsia risks include chronic HTN or kidney disease prior to pregnancy, obesity, women older than 40 years, multiple gestation, African American ethnicity, family history or preeclampsia, history of preeclampsia and preterm delivery at less than 34 weeks, history of preeclampsia in two or more number of pregnancies
- Nutritional support:
  - Avoid protein restriction.
  - Provide vitamins, folate supplement.
  - Iron supplement to keep serum ferritin levels of 200 to 300 µg/mL
  - Supplement calcium 1.5 to 2.0 g/d.
- Maintain Hb 10 to 11 g/dL with ESA. (Although anemia treatment goals are not defined in pregnancy, treatment with ESA appears to be safe.)

KRT in pregnancy

- KRT initiation is generally recommended at eGFR less than 20 mL/min/1.73 m^2 or BUN greater than 50 mg/dL.
- Increasing dialysis dose improves gestational age, live birth rates, and birth weight and reduces rates of maternal HTN and polyhydramnios.
- Earlier dialysis initiation and more intensive dialysis is associated with better maternal and fetal outcome.

HD in pregnancy

- HD is generally preferred to PD (Grade 2B).
  - Pregnancy rate is lower among PD than HD.
  - The rate of small for gestational age pregnancies has been reported to be lower in PD compared with HD patients.
- HD prescription in pregnancy
  - Duration of HD: Among individuals without residual kidney function, patients should be dialyzed at minimum 20 h/wk, but ideally greater than 36 hours. This may require at least 5 days of dialysis treatments weekly. Comparative data from a group of women from Canada who received intense HD (mean 43 h/wk) versus a group from the United States who received lower HD treatment duration (mean 17 h/wk) revealed higher live birth rates (85% vs 48%) and greater gestational age at delivery (36 vs 27 weeks).
  - Electrolytes: Avoid hypokalemia, hypocalcemia, hypophosphatemia. With more intensive HD regimen, hyperkalemia and hyperphosphatemia are less likely to occur.
  - UF: Rapid fluid shifts and volume removal should be avoided. Avoid hypotension because this can compromise uteroplacental circulation and induce uterine contractions.
  - Tight control of maternal weight and optimize UF to keep constant maternal/fetal hemodynamics to avoid growth retardation or poor outcomes. Consider intradialytic fetal monitoring.
  - HD goal: adequacy goals not well defined; most experts suggest achieving BUN less than 45 to 50 mg/dL. Some experts suggest BUN less than 35 mg/dL. Further studies are needed.

PD in pregnancy

- Perform low volume/more frequent exchanges, particularly during the third trimester. The use of a cycler may be required to provide

adequate therapy. The ideal prescription for PD in pregnancy remains to be defined.

- Avoid 4.25% dextrose solution to avoid rapid fluid shift and hypotension.

Fetal outcomes for mothers requiring KRT

- Conception prior to HD initiation is associated with higher live birth rates, but birth weight and gestational age are comparable to those conceived after HD initiation.
- Preterm delivery may reach 80% among mothers receiving KRT.
- The prevalence of small gestational age babies has been shown to be higher among mothers receiving PD compared with those receiving HD. A tendency for greater birth weight with more intense HD has been reported.

Medical Director Responsibilities and Conditions of Coverage

Qualifications of the Medical Director of the dialysis unit

- Board certified in internal medicine or pediatrics by a nationally recognized professional board
- Completion of a board-approved nephrology training program
- 12 months experience in caring for dialysis patients, including time spent in nephrology training
- Leadership skills to ensure a safe and professional working environment where high-quality and safe patient care can be easily delivered.

Responsibilities

- Developing, periodically reviewing, and approving a "Patient Care Policies and Procedures Manual"
- Delivery of patient care and outcomes
- Ensuring that all individuals who treat patients at the facility, including attending physicians and nonphysician providers, adhere

to all policies relative to:
  - Patient admissions
  - Infection control
  - Safety
- Reviewing adverse events and outcomes
- Ensuring that the interdisciplinary team adheres to discharge and transfer policies and procedures
- Reviewing and approving involuntary patient discharges
- Accountability to the governing body for the quality of medical care provided to patients
- Chair Quality Assessment and Performance Improvement (QAPI) program
- Staff education, training, and performance
- Emergency preparedness:
  - Plans for emergency preparedness that include fire, equipment or power failure, interruption of water supply, natural disasters (eg, fire, earthquakes)
  - Training and orientation in emergency preparedness to the staff that are assessed at least annually
  - Decide on specific emergency drugs to be available and describe these drugs in the facilities
- The medical director should devote sufficient time to ensure that safe and effective care is delivered to all patients. This requires the medical director be actively involved in the oversight of the facility, which includes:
  - Attending care plan meetings (if they have patients in the facility)
  - QAPI committee meetings
  - Guiding development of performance improvement/action plans
  - Assuring that staff are sufficiently trained to perform their assigned roles

- As a guide, each facility's financial cost report, filed with the CMS, considers the Medical Director role as 0.25 full-time employment.

Conditions of coverage for ESKD facilities refer to conditions that dialysis facilities must meet to be certified under the Medicare program. The established rules are focused on:

- The patient and the results of care provided to the patient
- Performance expectations for facilities
- Patient participation in their plan of care and treatment
- Preservation of strong process measures when necessary to promote meaningful patient safety, well-being, and continuous quality improvement.
- The final rule (Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Conditions for coverage for end-stage renal disease facilities. *Federal Register, 73*(73);20370-20484) reflects the advances in dialysis technology and standard care practices since the requirements were last revised in their entirety in 1976.

Infection control issues under conditions for coverage

- Preventive measures
  - Infection control training of staff and patients
  - Strict hand hygiene
  - Environmental cleaning and disinfection of dialysis stations
  - One-way flow of supplies and medications
  - Immunization for hepatitis B, influenza, and *pneumococcus*
- Routine surveillance
  - Routine serologic testing of hepatitis B and C
  - Infection surveillance (eg, catheter-related bacteremia)
- Isolation
  - Isolation of patients who are hepatitis B positive

CHAPTER 5

Hypertension

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HYPERTENSION BACKGROUND AND DEFINITIONS

Epidemiology

Hypertension (HTN) in the United States (US) (see the Centers for Disease Control and Prevention website: High blood pressure facts https://www.cdc.gov/high-blood-pressure/data-research/facts-stats/index.html)

Nearly half of the adults in the US (48.1%, 119.9 million) have HTN, defined as having systolic blood pressure (SBP) >130 mm Hg or diastolic blood pressure (DBP) >80 mm Hg, or taking antihypertensive medications.

HTN by gender: 50% of men and 44% of women have HTN.

HTN by race: In adults, HTN occurs in 56% of non-Hispanic blacks, 48% of non-Hispanic whites, 46% of non-Hispanic Asians, and 39% of Hispanics.

Geographic prevalence: HTN is most prevalent in the southeast and eastern urban regions of the US.

HTN management

- All adults with HTN are recommended by a clinician to undergo lifestyle modifications.
- Four in five adults with HTN are recommended by a clinician to take prescription medication(s).

HTN control

- Approximately 25% of adults with HTN have their HTN under control.
- Approximately 50% of adults with uncontrolled HTN have BP ≥140/90 mm Hg.

Clinical impact of HTN

- In 2021, HTN was a primary or contributing cause of 691,095 deaths in the US.
- HTN costs the US approximately $131 billion annually, averaged from 2003 to 2014.

Worldwide HTN

- Global age-standardized prevalence of HTN, defined as BP (SBP) >140/90 mm Hg, was 24% in men and 20% in women in 2015.
- The number of people with HTN has increased by 90% during the four decades studied, presumably due to population growth and aging.
- Prevalence of HTN decreased in high-income and increased in low-income countries in South Asia and sub-Saharan Africa, and remains persistently high in Central and Eastern Europe.

HTN Screening per U.S. Preventive Services Task Force (USPSTF)

- The USPSTF recommends screening for all adults ≥18 years of age.
- Initial screening: office BP measurement at brachial artery as well as ambulatory BP measurement (ABPM) or home BP monitoring using validated equipment
- Screening frequency
  - Annually for adults >40 years
  - Every 3 to 5 years for adults 18 to 39 years

BP Measurements

Standardized office or home BP measuring techniques: (1) no conversation, (2) no exercise, nicotine, or caffeine at least 30 minutes prior, (3) empty bladder, (4) place correct cuff size on bare arm, (5) support arm at heart level, (6) keep legs uncrossed, (7) support back and feet

Ambulatory BP measurements

Ideally, ABPM should be obtained along with office BP on every patient to address variations in BP over the day. In cases where ABPM is not available, home BP monitoring should be advised.

Automatic oscillometric BP (AOBP) office measurements: Generally done after 5-minute rest. The device provides the average of three to five consecutive BP readings at intervals of 1 to 2 minutes following a single activation. There is evidence to suggest that shorter rest periods and intervals between readings may be as accurate as ABPM.

Cuffless BP measuring devices (eg, smart phone application)

Calibration and accuracy studies are still needed prior to routine use.

Variability in BP measurements

- Casual office BP (defined as not following standardized techniques outlined earlier) is generally 5 to 10 mm Hg higher than standardized office or home BP, AOBP, and awake ambulatory BP.
- Standardized office BP may be lower than awake ambulatory BP.
- Out-of-office BP may provide better prediction of kidney disease progression and cardiovascular (CV) events than in office BP measurements among patients with chronic kidney disease (CKD).

Between-arm BP measurement differences

- Between-arm BP differences of 4 to 5 mm Hg occur in healthy people.

- Values >10 mm Hg should be considered for vascular assessment.
- Values >15 mm Hg are predictive of prevalent vascular disease and death.
- BP treatment should be based on higher BP arm.

Situations Where ABPM Should Be Considered

Uncertainty in the diagnosis of HTN

- Suspected white coat HTN (WCH) or masked HTN
- Hypotensive symptoms
- Autonomic dysfunction
- Episodic HTN
- Carotid sinus syncope
- Pacemaker syndromes
- Unexplained target organ damage (eg, left ventricular hypertrophy [LVH] without office HTN)
- Evaluation of BP changes in patients with paroxysmal nocturnal dyspnea and nocturnal angina

Optimizing treatment of HTN

- Apparent drug resistance (BP not at goal while seemingly being on maximal and optimal drug combination; WCH, noncompliance, proper BP measuring techniques, etc, have not been ruled out)
- Assess 24-hour BP control on once-daily medication.
- Safety of withdrawing antihypertensive medications
- Evaluation of antihypertensive drug therapy in clinical trials

Other

Evaluation of nocturnal BP dipper or riser as prognostic factor for target organ disease

BP Categorization for Nonpregnant Adults >18 Years of Age

BP categorization is based on the average of two or more properly measured readings obtained on at least two separate visits after initial screen.

Normal: SBP <120 mm Hg AND DBP <80 mm Hg

Elevated BP

- SBP 120 to 129 mm Hg AND DBP <80 mm Hg
- Pre-HTN category is no longer used.

Stage 1: SBP 130 to 139 mm Hg or DBP 80 to 89 mm Hg

Stage 2: SBP ≥140 mm Hg or DBP ≥90 mm Hg

HTN defined based on ABPM

- 24-hour average >130/80 mm Hg
- Daytime (awake) average >135/85 mm Hg
- Nighttime (asleep) average >120/70 mm Hg

BP Goals

2017 Hypertension Clinical Practice Guidelines (ACC/AHA)

- The 2017 Hypertension Clinical Guidelines relies on average BP readings.
- BP should be categorized as normal, elevated, or stage 1 or 2 HTN.
- Out-of-office BP measurements are recommended to confirm the diagnosis of HTN and titrate BP lowering medication.

Goal BP

American College of Cardiology/American Heart Association (ACC/AHA)
SBP <130 mm Hg or even <120 mm Hg for those in good health if well tolerated
Kidney Disease Improving Global Outcomes (KDIGO) HTN guideline 2021
SBP goal <120 mm Hg for all patients with CKD

Summary of Systolic blood PRessure INTervention trial (SPRINT)

Multicenter, randomized, controlled trial of intensive versus standard BP control

- 9,361 persons with SBP ≥130 to 180 mm Hg at increased risk for cardiovascular disease (CVD) but without diabetes mellitus (DM) were enrolled and randomized to SBP control <120 mm Hg (intensive) or <140 mm Hg (standard control).
- Inclusion: age ≥50 years with SBP ≥130 mm Hg and ≥1 of the following: history of CVD, CKD G3, intermediate to high risk for CVD other than stroke, or age ≥75 years

Final report (N Engl J Med 2021)

- Baseline mean age 67.9 years, 28.2% were ≥75 years old; 28.3% had CKD; 20.0% had CVD
- Follow-up: median follow-up 3.33 years
- Primary composite outcome (myocardial infarction, other acute coronary syndromes, heart failure [HF], or death from CV causes): 1.77% versus 2.4% per year, intensive versus standard BP control, respectively
- All-cause mortality: 1.06% versus 1.41% per year
- For individuals with CKD, there was no difference in the incidence of composite kidney outcome (decrease in estimated glomerular filtration rate [eGFR] of 50% or more or end-stage kidney disease [ESKD]). However, for individuals without CKD, a 30% decrease in eGFR to <60 mL/min/1.73 m^2 was more common in the intensive treatment group compared with the standard treatment group.

There were also higher rates of serious adverse events related to acute kidney injury (AKI) in the former group.

- Adverse effects: Hypotensive and syncopal episodes (but not injurious falls), electrolyte disturbances (hypokalemia, hypo- and hypernatremia), and AKI were more common in the intensive group.
- Note that BP measurements in the SPRINT were based on automated office BP measurements, which are lower than office BP measurements performed by providers.

Management

Nonpharmacologic therapy (applicable to everyone as safely tolerated)

Weight reduction

- Target ideal body weight or weight loss of at least 1 kg
- SBP may reduce by 1 mm Hg/kg weight loss.
- Pharmacologic strategies if safely tolerated (eg, orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide)

Adopt Dietary Approaches to Stop Hypertension (DASH)-like eating plan

- Encourage diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced saturated and total fat.
- SBP may decline by 8 to 14 mm Hg.

Sodium restriction

- <1,500 mg/d; aim for ≥1,000 mg/d reduction in most adults.
- SBP may reduce by 2 to 8 mm Hg.

Increase potassium intake

- 3,500 to 5,000 mg/d unless patient has problems with hyperkalemia (eg, if feasible, use salt substitutes, KCl + NaCl combination instead of regular salt with NaCl alone)
- SBP may reduce by 4 to 5 mm Hg.

Physical activity

- Regular aerobic, dynamic resistance, or isometric resistance activity, for example, 30-minute brisk walk daily, most days of the week, or 150 min/wk
- SBP may reduce by 4 to 9 mm Hg.

Moderation of alcohol consumption

- <2 drinks daily in most men, <1 drink daily in women and lightweight persons
- SBP may reduce by 2 to 4 mm Hg.

Smoking cessation

For overall CV risk reduction, stop smoking.

Addition of pharmacologic therapy is recommended for

HTN stage 2 or
HTN stage 1 if

- Known atherosclerotic cardiovascular disease (ASCVD) or 10-year ASCVD risk ≥15%
- DM type 2 or
- CKD

Follow-up

- Patients with elevated BP or stage 1 HTN not on drug therapy should have their BP reassessed every 3 to 6 months.
- Patients initiated on antihypertensive medications should be monitored monthly until BP is controlled and stable.

Other considerations

- For patients with asymptomatic mild or moderate aortic stenosis with normal left ventricular systolic function: BP target of 130 to 139/70 to 89 mm Hg is reasonable. A post hoc analysis of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial revealed the lowest all-cause mortality rate for patients in the BP range of

120 to 139/70 to 79 mm Hg. All-cause mortality was significantly higher in patients with average SBP <120 mm Hg and average DBP ≥90 mm Hg.

- For patients >65 years old, be cautious not to lower DBP <65 mm Hg because this has a suggested association with increased stroke risk.
- For those with a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

Definitions of Terms and Concepts Relating to HTN

White coat HTN

Definition: WCH refers to having home or daytime ambulatory BP <130/80 mm Hg but office BP >130/80 mm Hg after 3 months of diet and lifestyle modification.

Prevalence of WCH among patients with CKD has been estimated to range from 2% to 41%.

Clinical significance of WCH

- Some studies revealed increased left ventricular mass index with WCH.
- Affected individuals may have impaired diastolic function and higher levels of catecholamines, renin/aldosterone, low-density lipoproteins.
- Conversion to sustained HTN occurs in 1% to 5% annually.

Treatment: Start antihypertensives if office BP is persistently elevated and with evidence of target organ damage, for example, LVH on electrocardiogram (ECG) or echocardiogram.

Masked HTN

Definition: Office BP is lower than that measured in out-of-office setting (opposite of WCH).

Prevalence in the general population is estimated at 10% to 20% and in patients with CKD at 20% to 50%.
Clinical significance of masked HTN

- A systematic review of published literature from 2000 to 2018 reported similar risks of fatal and nonfatal cardiac and CV events among patients with masked HTN compared with those with sustained HTN, hazard ratio (HR) ~2.1 versus 2.3.
- International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome, 738 treated white patients, aged 30 to 90, whose office BPs were controlled: Combined daytime and nighttime masked HTN, but not nighttime or daytime alone masked HTN, was associated with a significant increase in CV events, HR of 2.29.

Treatment: Initiate antihypertensive therapy if 24-hour ambulatory BP is elevated and there is evidence of target organ damage.

Sustained HTN

HTN in both in- and out-of-office settings

Pseudo-HTN

Definition: Pseudo-HTN is defined as having cuff DBP >10 to 15 mm Hg higher when compared with intra-arterial pressure because of excessive atheromatosis and/or medial hypertrophy in arterial tree.
Diagnosis: may be diagnosed by Osler maneuver

- Inflate BP cuff above SBP (detected by loss of pulse with auscultation).
- Osler maneuver is positive when either brachial or radial artery remains palpable despite loss of pulse by auscultation.

Management of BP should be based on intra-arterial value.

Isolated systolic HTN (ISH)

- Occurs with stiffening of large arteries leading to reduced vessel capacitance and acceleration of pulse wave velocity, hence widening of pulse pressure
- Increase in SBP continues throughout life, in contrast to DBP, which increases and peaks by age of 50 then decreases later in life.
- After 50 years, SBP is more important than DBP.

Isolated diastolic HTN (IDH)

Definition: having DBP ≥80 mm Hg with SBP <130 mm Hg (per 2017 ACC/AHA)

- More common in young overweight/obese males
- More common than combined systolic and diastolic HTN (SDH) and ISH in individuals <40 years of age. IDH is rare in individuals >60 years old.

Clinical significance of IDH: unclear, data appear to be conflicting

- IDH had no increase in all-cause mortality: Finland study, 3,267 healthy men 32 to 45 years old
- IDH had no increased risk for CV outcomes: cross-sectional analyses of National Health and Nutrition Examination Survey (NHANES) 2013 to 2016; longitudinal analyses of the Atherosclerosis Risk in Communities study
- IDH had increased risk of CVD:
  - South Korea–based study, 6.4 million, aged 20 to 39: ISH, IDH, and combined SDH all had a 30% to 60% higher risk for CVD composite (hospitalization for heart attack, HF, or stroke, and CVD-related deaths).
  - World Health Organization European study Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA), >107,000 individuals, aged 19 to 97: Elevations in DBP among individuals <50 years of age were predictive of CVD outcome.

- Rate of progression or conversion to SDH was 55% in 6.7 years in the Framingham Heart Study.

Management of IDH

- Focus on salt restriction and weight loss, the latter if overweight or obese.
- Pharmacologic antihypertensive therapy if end-organ damage, that is, proteinuria or left ventricular HTN on ECG, or hypothyroidism. Hypothyroidism is associated with more pronounced diastolic than SBP rise.
- If no specific indication for any antihypertensive class, patients with IDH tend to respond well with just one agent, typically better with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) than dihydropyridine calcium channel blocker (CCB).

Drug-resistant HTN

Definitions

- BP is not at goal despite optimal doses (optimal dose, defined as >50% of maximal dose recommended for treatment of HTN) of three different appropriate (eg, first-line) antihypertensive drug classes, ideally one class being a diuretic.
- Alternatively, BP is at goal with optimal doses of four appropriate antihypertensive drug classes, ideally one class being a diuretic.

Refractory HTN

Definition: BP not controlled despite being on ≥5 drugs including a diuretic

Apparent (drug)-resistant HTN

Definition: Patients with *apparent* "drug-resistant HTN" are those who meet criteria for drug-resistant HTN but have NOT been ruled out for proper BP techniques, WCH, noncompliance, improper BP medication regimens (eg, using several vasodilators in a patient with

increased heart rate without a β-blocker, using multiple sympatholytic drugs without any vasodilator, or using multiple drugs with reflex salt retention but without a diuretic).

Pseudoresistant HTN

Definition: patients who initially meet the criteria for "drug-resistant HTN" but are later proven to fail meeting the same criteria following proper BP measuring techniques, ABPM, and/or compliance with proper BP medication regimens

Apparent resistant HTN may be seen in 15% of the population treated for HTN in the US but ~50% of these patients have pseudoresistant HTN. True resistant HTN is approximated at 5% of treated hypertensives.

Hypertensive urgency

Definition: severe HTN, typically with SBP >180 mm Hg or DBP >110 mm Hg, with or without symptoms such as severe headaches, dyspnea, or anxiety, but *without* ongoing end-organ damage

Hypertensive emergency

Definition: severe HTN, typically with SBP >180 mm Hg or DBP >110 mm Hg, in symptomatic patients (eg, severe headaches, chest pain, neurologic deficits) *with* ongoing end-organ damage

Dippers and risers

Definitions

- Dippers are individuals who experience a physiologic nocturnal fall in BP of >10% compared with daytime BP. The proportion of dippers decreases with increasing CKD stage.
- Risers experience a physiologic nocturnal increase in BP of >10% compared with daytime BP. The proportion of risers increases with increasing CKD stage.

Clinical significance

It has been suggested that non-dippers or risers, particularly in association with elevated absolute nighttime BP, may predict end-organ damage and adverse CV events. A Japanese study involving 485 elderly individuals, with average age of 83 years, revealed a 1.8-fold increased risk for CVD events among risers when compared with dippers.

Essential (Primary) HTN

Pathogenesis of essential HTN

- Increased sympathetic nerve activity (SNA) and responsiveness to SNA
- Increased angiotensin II (Ang II) activity and mineralocorticoid excess

Risks of essential HTN

- Genetics: 2-fold risk if both parents have HTN
- Reduced nephron mass due to immature birth, intrauterine developmental abnormality (eg, maternal drug use, malnutrition), and postnatal disturbances (eg, malnutrition, infections)
- Black ethnicity (more common and severe compared with non-blacks). APOL1 risk alleles have been shown to be associated with increased SBP and earlier onset of HTN in young adults of African ancestry.
- Lifestyle associated: high salt intake, excess alcohol consumption, physical inactivity, vitamin D deficiency. Fructose intake, thus far, has not been proven to increase HTN risk.
- Metabolic: dyslipidemia, independent of obesity

EVALUATION OF HTN

Routine Evaluation in Patients With HTN

In addition to obtaining a complete medical history and performing a thorough physical exam, a review of all medications is warranted.

Screen for drug-induced HTN

Prescribed medications

- Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors
- Oral contraceptives (estrogens, progestins)
- Glucocorticoids, mineralocorticoids, anabolic androgenic steroids
- Cyclosporine (CSA) and tacrolimus
- Antidepressants (monoamine oxidase inhibitors, serotonin-norepinephrine (NE) uptake inhibitor [venlafaxine, sibutramine])
- Erythropoiesis stimulating agents (reduced nitric oxide synthesis, increased entholin-1)
- Vascular endothelial growth factor (VEGF) inhibitors, for example, sunitinib (downregulate nitric oxide expression)

Selected over-the-counter dietary supplements and medications

- Sympathomimetics (decongestants, anorectics)
- Ephedra, ma huang, bitter orange, ginseng, yohimbine
- Licorice (including some chewing tobacco)

Common drinks/recreational drugs

- Caffeine (small and transient increase in BP)
- Excess alcohol intake
- Cocaine, amphetamines, methamphetamines, other illicit drugs

Recommended routine testing: lipid profile, kidney function, urinalysis, fasting blood glucose, hemoglobin A1c, complete blood count, ECG for LVH, thyroid-stimulating hormone

Optional testing: echocardiogram, uric acid, urine albumin to creatinine ratio

Clinical clues that should prompt evaluation for secondary HTN

Age related

- Onset at age <30 years in nonobese, non-black individuals without other HTN risk factors
- Onset of diastolic HTN in patients ≥65 years

Acute changes in BP

- Abrupt-onset HTN
- Exacerbation of previously controlled HTN

HTN severity

- Drug-resistant or refractory HTN
- Malignant or accelerated HTN (eg, hypertensive urgency or emergency)
- Target organ damage out of proportion to the degree of HTN

Unprovoked or severe hypokalemia (eg, hypokalemia in the absence of diuretic use)

Presence of signs/symptoms related to specific hypertensive conditions

Family history of monogenic HTN

SECONDARY CAUSES OF HTN

Secondary causes of HTN and their corresponding evaluations are summarized in **Figure 5.1** and **Table 5.1**, respectively.

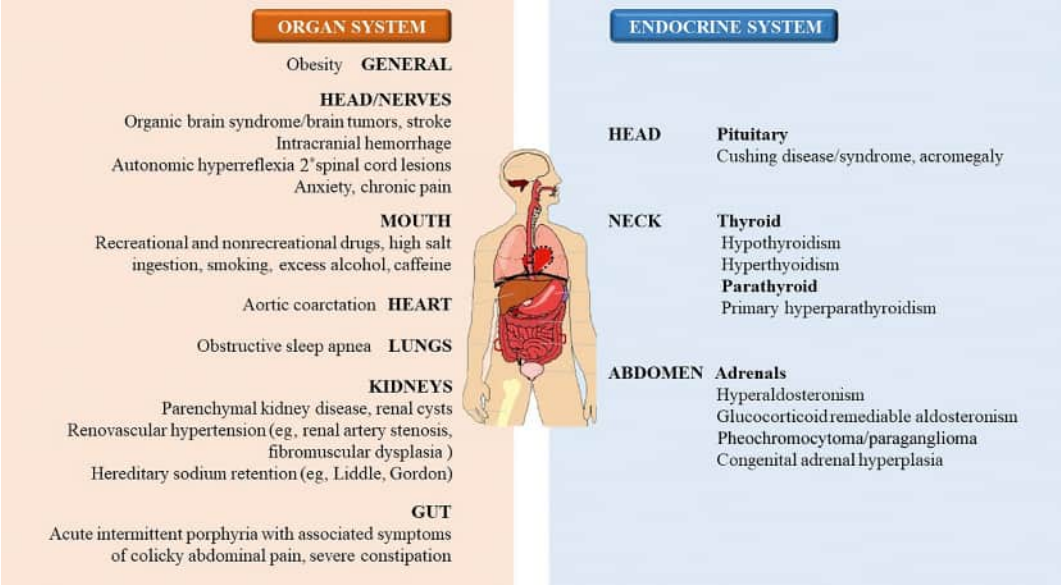


FIGURE 5.1 Secondary causes of hypertension categorized by organ and endocrine systems.

Table 5.1 Evaluation of secondary hypertension

		Conditions and clinical clues	Screening tests
Organ system	Oral	Prescribed, OTC, or recreational drugs, salt	24-h urine creatinine and Na^+; drug screen
	Brain	Brain trauma, psychiatric disorders, pain, anxiety, autonomic dysreflexia	Brain CT or magnetic resonance imaging
	Heart	Coarctation of aorta: midback continuous murmur; rib notching on CXR	BP measurements higher in upper than lower extremities; echocardiogram
	Lung	Obstructive sleep apnea	Sleep study
	Kidney	Any kidney disease	Urinalysis, uPCR, kidney ultrasound
		Liddle syndrome	Low to normal PRA and aldosterone level; Genetic analysis

		Conditions and clinical clues	Screening tests
		Apparent mineralocorticoid excess; licorice	Urine free cortisol to cortisone ratio; Genetic analysis
		[a]Mineralocorticoid receptor activating mutation: worse HTN with pregnancy	MRA may worsen HTN; genetic analysis
		Glucocorticoid remediable aldosteronism	↓PRA and ↑plasma aldosterone, ↑18-hydroxy- and 18-oxo-cortisol, ↑ACTH
		Atherosclerotic disease: renal artery stenosis Young females: fibromuscular dysplasia	Renal arterial duplex screening Magnetic resonance angiogram or CTA
	Neuro/GI	Acute intermittent porphyria: intermittent abdominal pain, constipation, urinary retention, dark urine, tachycardia, sweating, neuropsychiatric disorders	Urinary porphobilinogen spot test
Endocrine system	Pituitary	Acromegaly: skull, hands, feet enlargement, excessive sweating, carpal tunnel, headaches	Growth hormone, insulin-like growth factor-1
		Cushing disease/syndrome: central obesity, buffalo hump, proximal weakness, glucose intolerance, hirsutism	24-h urine free cortisol; bedtime salivary cortisol levels; 1 mg overnight dexamethasone suppression test
	Thyroid	Hypothyroid: hypothermia, bradycardia, ±low pulse pressure Hyperthyroid: tachycardia, ± ↑pulse pressure	TSH; also check free thyroxine if concerns for hyperthyroidism or central hypothyroidism

		Conditions and clinical clues	Screening tests
	Parathyroid	Hypercalcemia, hypophosphatemia	Serum Ca^{2+}, PO_4^{2-}, PTH levels
	Adrenal	Primary aldosteronism: hypokalemia, metabolic alkalosis, arrhythmias, AFib	↓PRA and ↑aldosterone level
		Congenital adrenal hyperplasia: incomplete masculinization; 1° amenorrhea	Deoxycorticosterone, 17-hydroxyprogesterone levels
		Pheochromocytoma/PG: paroxysmal HTN, headaches, palpitations, pallor, sweating	Plasma fractionated metanephrines (see text)

[a]Also known as syndrome of apparent mineralocorticoid excess or Geller syndrome

Abbreviations: ACTH, adrenocorticotropic hormone; AD, autonomic dysreflexia; AFib, atrial fibrillation; BP, blood pressure; CAH, congenital adrenal hyperplasia; CT, computed tomography; CTA, computed tomogram angiography; CVD, cardiovascular disease; CXR, chest radiograph; ENaC, epithelial sodium channel; GI, gastrointestinal; HTN, hypertension; MRA, mineralocorticoid receptor antagonists; neuro/GI, neurological/gastrointestinal system; OTC, over the counter; PG, paraganglioma; PRA, plasma renin activity; PTH, parathyroid gland; uPCR, urine protein-creatinine ratio; TSH, thyroid-stimulating hormone;.

Obesity

Factors that may contribute to HTN in obesity

Hyperleptinemia, hyperinsulinemia, endothelial dysfunction, sympathetic nervous system (SNS) activation, kidney injury, hyperaldosteronism driven by circulating oxidized fatty acids (linoleic acid) or uric acid, obstructive sleep apnea (OSA)

Bariatric surgery

- BP reduction correlates with degree of weight loss, not type of bariatric surgery.
- HTN relapse rates are high for either Roux-en-Y gastric bypass or vertical sleeve gastrectomy despite great weight loss. Continuing

lifestyle modifications and pharmacologic therapy are needed for maintenance of BP control.

Obstructive sleep apnea

- OSA occurs in 30% of patients with HTN and up to 70% to 90% of patients with resistant HTN.
- The association between OSA and HTN is dependent on OSA severity and presence of obesity. Association is not significant in individuals with body mass index (BMI) <25 kg/m^2 (NHANES data).
- Continuous positive airway pressure (CPAP) ventilation of >4 hours duration during sleep can reduce SBP by 2 to 3 mm Hg (ACC/AHA 2017 Hypertension Guidelines).
- Many patients with OSA may have activated renin-angiotensin-aldosterone system (RAAS), hence sodium and water retention leading to upper airway edema, predisposing to upper airway collapse in the supine position. For this reason, mineralocorticoid receptor antagonists (MRAs) may be a beneficial class of antihypertensive agent. The Endocrine Society (ES) guidelines advise screening for primary aldosteronism (PA) for all patients with HTN and OSA.
- β-Blockers may also be effective antihypertensive agents due to sympathetic overactivity.
- Data on renal denervation for BP improvement remain conflicting. Ongoing trials may provide better answers. Concerns regarding the renal denervation procedure include promotion of renal artery atherogenesis and interference with denervated kidney to tolerate insults such as volume depletion, infection, trauma, or drug exposure.

Neurogenic HTN Management per AHA/American Stroke Association

Understanding cerebral blood flow and perfusion pressure

- Cerebral blood flow = cerebral perfusion pressure (CPP) ÷ cerebrovascular resistance, where
- CPP = mean arterial pressure (MAP) − intracranial pressure (ICP). CPP should be >60 mm Hg.

HTN after stroke

Contributing factors: Cushing reflex, catecholamine and cortisol release, lesion involving brainstem or hypothalamus, nonspecific response, acute stress

For acute ischemic stroke patients receiving thrombolytic therapy

- Before thrombolytics: Lower BP if SBP >185 mm Hg or DBP >110 mm Hg.
- After thrombolytics: Lower BP if SBP >180 mm Hg or DBP >105 mm Hg for the first 24 hours.
- Early treatment of HTN may be indicated in the presence of certain comorbid conditions (eg, HF, aortic dissection, acute myocardial infarction).

For acute ischemic stroke patients NOT receiving thrombolytic therapy

Antihypertensive medications should be withheld unless SBP ≥220 mm Hg or DBP ≥120 mm Hg.

Notes to consider in the management of HTN after stroke

- If BP lowering is indicated as outlined earlier, lower BP cautiously by about 15% during the first 24 hours after onset of stroke.
- Patients with acute ischemic stroke and BP <180/105 mm Hg in the first 72 hours do not seem to benefit from introduction or reintroduction of antihypertensive drugs.
- Antihypertensive therapy after 72 hours should be considered for those who remain hypertensive and stable.

HTN in acute intracerebral hemorrhage

- When SBP is between 150 and 220 mm Hg, acute BP lowering may be effective in improving functional outcome and is safe.
- When SBP is >220 mm Hg, it may be reasonable to lower BP with continuous intravenous (IV) infusion of an antihypertensive agent with frequent BP monitoring.
- Most common agents used: IV labetalol and nicardipine

HTN after carotid endarterectomy (CEA) and endovascular procedures (eg, angioplasty, stenting)

Contributing factors: carotid baroreceptor impairment after surgical manipulation, elevated catecholamine levels, activation of trigeminovascular axon reflex

Carotid hyperperfusion syndrome following CEA

- Occurs during the first week after surgery
- Cerebral hyperperfusion is defined as having a postoperative increase in cerebral blood flow of >100% compared with preoperative flow, an increase that may only be ~20% compared with the "normal" contralateral side.
- Ipsilateral: pulsatile headaches, seizures, intracranial hemorrhage, cerebral edema
- Contralateral: neurologic symptoms
- Management:
  - Continuous intra- and postoperative BP monitoring
  - Strict BP control with SBP <120 mm Hg
  - Preferred agents: IV labetalol or clonidine
  - Avoid vasodilators such as nitroglycerin, sodium nitroprusside

Autonomic dysreflexia: HTN after spinal cord injury affecting the sixth or higher level thoracic spinal nerve

- Defined as SBP increase of >20% *from baseline* with associated change in heart rate (brady- to tachycardia), and at least one of the following: headache, facial flushing, blurry vision, stuffy nose,

sweating, piloerection. Flush sweaty skin above lesion levels is due to brainstem parasympathetic activation.

- Occurs in up to 70% of patients with spinal injury affecting the sixth or higher level thoracic spinal nerve
- During labor and delivery, autonomic dysreflexia can precipitate in up to 90% in affected women. Use of epidural or spinal anesthesia may reduce risk.

Pathophysiology

- Immediately following spinal injury, there is a loss of supraspinal sympathetic control, an initial period of muscle flaccidity, bradycardia, and hypotension.
- Weeks to months following injury, there is extrajunctional sprouting of α-receptors, denervation hypersensitivity, impaired presynaptic uptake of norepinephrine (NE), and derangement of spinal glutaminergic interneurons.
- Presence of any noxious stimulus below neurologic level of the lesion thereafter triggers a spinal reflex arc that results in increased sympathetic tone and HTN.
- Common noxious stimuli are from urinary overdistention and fecal impaction. Others: Sympathomimetic medications and sildenafil citrate are used for sperm retrieval.

Management

- Preventive measures: good bowel, bladder, and skin care
- Treatment:
  - Position patient upright to precipitate orthostatic BP.
  - Remove noxious stimuli (eg, tight clothing, devices, fecal disimpaction, bladder catheterization as applicable).
  - Medications: Select fast-acting, short-lived agents for persistent SBP elevation >150 mm Hg. Consider other noxious stimuli and hospitalization if there is no resolution.

Coarctation of Aorta

- Narrowing of the descending aorta, typically distal to left subclavian artery
- Congenital coarctation of aorta can be associated with other congenital cardiac defects including bicuspid aortic valve, subaortic stenosis, and patent ductus arteriosus.
- Diagnosis: echocardiogram

Parenchymal Kidney Disease

Parenchymal kidney disease is the most common cause of secondary HTN.

Chronic kidney disease

- HTN occurs in >80% of individuals with CKD.
- Contributing factors: volume expansion, RAAS and SNS activation, increased endothelin production, reduced endothelin-derived production of vasodilators, arterial stiffening
- Management should include a diuretic (thiazide or loop diuretic depending on volume status).

Proteinuria and HTN

- Proteinuria with loss of plasminogen in urine leads to the formation of plasmin by tubular urokinase-like plasminogen activator. Plasmin directly stimulates the distal tubular sodium epithelial channel (ENaC) via the proteolytic cleavage of ENaC extracellular α- and γ-subunits. Activated ENaC enhances sodium reabsorption.
- Consider amiloride (ENaC inhibitor) in patients with proteinuria and salt-sensitive HTN.

Simple renal cysts and HTN

- HTN is thought to be due to cyst compression on adjacent renal parenchyma resulting in focal ischemia and RAAS activation.

- HTN is associated with increased number of cysts (≥2) and cystic size >1.4 to 2.0 cm.
- Management:
  - Use of renin-angiotensin-aldosterone blockers may be beneficial.
  - Cyst decompression (anecdotal reports)

Renovascular HTN

Clinical manifestations common to both unilateral and bilateral renal artery stenosis

- New-onset HTN
  - HTN typically occurs with renal artery stenosis ≥70%, not when stenosis is below 60%.
  - Less than 60% stenosis (or <10%-20% pressure gradient drop across stenotic lesion) does not cause measurable reduction in either pressure or flow. In mild stenosis, there is no need for activation of vasopressors to restore renal artery perfusion, thus there is absence of HTN.
- Abdominal systolic-diastolic bruits (sensitivity 39%-63%, specificity 90%-99%)
- Paroxysmal symptoms due to SNS activation
- Loss of nocturnal BP dipping
- Accelerated end-organ damage including LVH, microvascular disease, renal fibrosis
- Long-term glomerular hyperfiltration and development of focal segmental glomerulosclerosis (FSGS) may occur in the contralateral kidney in unilateral renal stenosis.

Diagnostic studies (per American College of Radiology [ACR] 2017)

- For patients with high index of suspicion of renovascular HTN and normal kidney function, contrast-enhanced computed tomography

(CTA) and magnetic resonance angiography (MRA) are preferred modalities. Ultrasound with Doppler is also an effective modality.

- For patients with high suspicion of renovascular HTN with eGFR <30 mL/min/1.73 m^2, ultrasound with duplex Doppler is the preferred modality.
- Captopril renal scintigraphy may be performed in selected cases but is not routinely considered the imaging study of choice.

Notes about imaging studies in diagnosing renovascular HTN

Renal arterial Doppler (ultrasonography)

- Most effective for detection of lesions in proximal main renal artery (good for proximal renal artery stenosis due to atherosclerotic disease but not a great study for fibromuscular dystrophy [FMD] where lesions are typically more distal)
- Peak systolic velocity >200 cm/s on duplex Doppler suggests stenosis of at least 60%.
- Advantages: inexpensive, readily available
- Disadvantages: does not provide functional information, sensitivity depends on skill of operator and patient's body habitus

MRA versus CTA imaging studies

- Both modalities are more accurate in diagnosing proximal rather than distal lesions.
- Stenosis of ≥70% to 75% in one or both renal arteries suggests renovascular HTN.
- In general, CTA depicts branch renal arteries better than MRA.

ACEi (captopril) renal scintigraphy

- May be the appropriate modality in selected cases
- Provides information on renal blood flow (uptake/appearance of isotope phase) and filtration (excretory phase). Delayed excretory phase following captopril administration suggests significant role of Ang II in maintaining GFR.

- Advantages:
  - High negative predictive value, that is, negative test essentially rules out clinically significant renal artery stenosis.
  - Provides relative function of each kidney prior to invasive intervention
- Disadvantages: Sensitivity and specificity of captopril renal scintigraphy are reduced in patients with bilateral renal artery stenosis, impaired kidney function, or urinary obstruction.

Arteriography

- Considered the gold standard
- Requirement for high-contrast-dose injection into the inferior vena cava (IVC) or right atrium renders this modality "usually not appropriate" as a screening imaging study for renovascular HTN per ACR.

Unilateral stenosis, aka 2-kidney-1-clip model

Pathogenesis of HTN

- The reduced renal perfusion pressure in the stenosed kidney leads to RAAS activation. Increased Ang II and aldosterone increase renal perfusion pressure and sodium retention.
- The normal contralateral kidney undergoes pressure natriuresis to restore sodium and volume balance, thereby counteracting the stenosed kidney's attempt to improve its own perfusion. Continued RAAS activation by the stenosed kidney leads to Ang II–dependent HTN and aldosterone-induced renal K^+ and H^+ secretion, resulting in hypokalemia and metabolic alkalosis.

Clinical implication for unilateral renal artery stenosis

- RAAS inhibition is expected to be effective in reducing BP.
- RAAS inhibition also enhances lateralization with nuclear testing by reducing GFR in the stenotic kidney (captopril renal scan).

Conditions equivalent to unilateral stenosis

- Unilateral FMD, atherosclerotic disease, renal artery aneurysm/dissection, renal artery trauma or occlusion by embolus

or thrombus, arteriovenous fistula, vasospasm, aortic dissection affecting renal ostium or aortic stent occluding origin of renal artery

- Extrinsic compression (eg, tumor) on one renal artery, "Page" kidney (perinephric compression, eg, large capsular hematoma, perinephric fibrosis)

Bilateral renal artery stenosis, aka 1-kidney-1-clip model

Pathogenesis of HTN

- Both kidneys are exposed to reduced perfusion pressures.
- There is no "normal non-stenotic kidney."
- Initial activation of SNS and RAAS leads to sodium and water retention. Since there is no "normal kidney" to excrete the sodium and water retained, volume overload eventually develops, which leads to subsequent inhibition of RAAS.
- Unlike unilateral renal artery stenosis, HTN in bilateral renal artery stenosis is volume dependent, not RAAS dependent.

Clinical implications

- Patients can be highly salt-sensitive and easily develop "flash pulmonary edema" following a high-salt diet.
- Diuretics may be more effective as primary antihypertensive agent than RAAS inhibitors in patients with bilateral renal artery stenosis. However, RAAS inhibitors may be effective after euvolemia has been achieved (ie, RAAS activation recurs after the negative feedback from volume expansion has been removed).
- Since RAAS is inhibited by volume expansion, patients with bilateral renal stenosis or an equivalent typically do not develop hypokalemia and metabolic alkalosis. In fact, the opposite, hyperkalemia and metabolic acidosis, may be present.

Clinical conditions equivalent to bilateral renal artery stenosis

- Bilateral renal atherosclerotic disease or FMD, stenosis/arterial anomaly of solitary kidney

- Significant coarctation of aorta or any flow-limiting lesions (eg, atheroembolic disease [**Chapter 11: Acute Kidney Injury/ICU Nephrology**], aneurysms, extrinsic mass compression) of suprarenal abdominal aorta
- Renal artery vasculitis

Atherosclerotic renal artery stenosis

Atherosclerotic plaque formed from the first 1 to 2 cm of renal artery or from aorta extending into renal ostium (more proximal involvement compared with FMD)

Epidemiology of atherosclerotic renal artery stenosis

- Seen in 10% to 40% of patients undergoing coronary angiography
- Similar prevalence in African Americans and Caucasians in one study cohort involving 870 patients >65 years old
- Autopsy series: overall prevalence of 4% to 20%; 25% to 30% in those >60 years old, 40% to 60% in those >75 years old
- Estimated to contribute to kidney function decline in 15% to 22% of patients with ESKD

Clinical clues to the presence of ischemic renal disease due to atherosclerosis

- Asymmetry of kidney size
- AKI following use of ACEi or ARB due to acute reduction in intraglomerular filtration pressure (due to loss of Ang II–dependent efferent vasoconstriction to maintain intraglomerular filtration pressure)
- AKI following acute systemic BP reduction with any other hypertensive agents: This is due to the loss of minimal renal artery pressure required to maintain glomerular filtration by autoregulation.
- Flash pulmonary edema, more common in bilateral stenosis
- Consider renal stenosis in patients with known or at increased risk for atherosclerotic disease and unexplained kidney function

decline.

Management of atherosclerotic renal artery stenosis

- Medical therapy:
  - Diuretics if volume overloaded
  - RAAS inhibition as safely tolerated (Serum creatinine [SCr] increases less than 20%-30% from baseline are acceptable.)
  - Use of other agents as needed to control BP
  - Daily aspirin if safely tolerated
  - Statin as tolerated, particularly if hyperlipidemia and/or CKD and >50 years of age
  - Smoking cessation if applicable
- Invasive therapy for renal artery stenosis from atherosclerosis:
  - There is no evidence of renal or CV benefits with invasive therapy compared with conservative medical therapy in individuals with stable kidney function and BP. See **Appendix A5.1** for clinical trials.
  - However, invasive therapy may be considered in younger patients with low comorbidities and rapidly progressive disease (ie, significant AKI with either RAAS inhibition or achievement of BP control), failure to achieve goal BP despite being on appropriate medical therapy, associated acute "flash pulmonary edema," and/or significant stenosis of a solitary kidney.
  - Renal artery stenting versus surgical revascularization: Surgical revascularization is reserved for patients with technically challenging lesions or associated severe aortic disease.
  - Contraindications to invasive therapy: advanced kidney disease (eg, SCr >3-4 mg/dL, kidney length <8-8.5 cm), poor surgical candidate, or low life expectancy

NOTE

- Atherosclerotic renal artery stenosis typically affects the proximal 1 to 2 cm of the renal artery from aorta, FMD involves the distal one-half to one-third of the renal artery, and polyarteritis nodosa involves multiple aneurysmal

dilations within the kidneys (**Figure 5.2**). Depending on the severity, all three conditions can present with HTN.

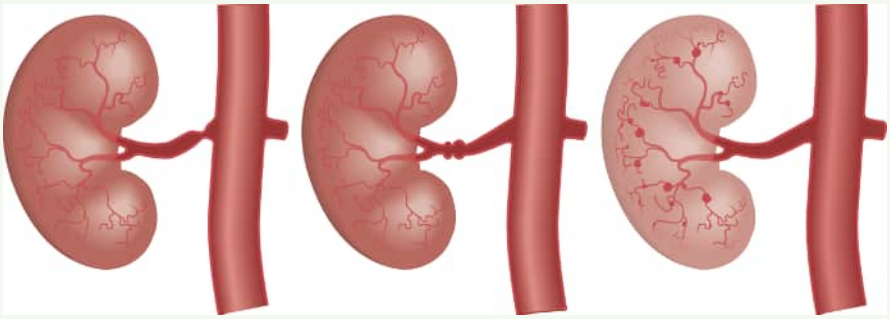


FIGURE 5.2 Renal artery stenosis, fibromuscular dysplasia, polyarteritis nodosa. Renal artery stenosis typically occurs within 2 cm from the aorta. Fibromuscular dysplasia typically occurs at the distal half to third of the renal artery. Polyarteritis nodosa occurs within the kidneys. Depending on the severity, all three conditions can present with hypertension.

- Most patients with renovascular HTN do not develop AKI with ACEi/ARB because:
  - In unilateral renal artery stenosis, the normal contralateral kidney may still have adequate function to mask any reduced filtration pressure in the affected kidney by ACEi/ARB.
  - In bilateral renal artery stenosis, Ang II is suppressed due to sodium retention. Hence, ACEi/ARB does not directly reduce glomerular filtration pressure.
  - Those with AKI with ACEi/ARB tend to have other additional source(s) contributing to reduced renal perfusion, for example, volume depletion, poor cardiac function.

Fibromuscular dysplasia

Nonatherosclerotic arteriopathy affecting large and medium-sized arteries, typically mid- to distal vessel beyond the first 2 cm from aorta (see **Figure 5.2**)

Epidemiology

- Prevalence of clinically significant renovascular FMD is 4/1,000, cerebrovascular involvement 1/1,000 (may present with carotid flow abnormalities, stroke).
- May be seen in up to 3% to 6% in normotensive individuals
- Familial presentation in 10% of cases, thought to be autosomal dominant

Clinical manifestations

- Commonly seen in young (15-50 years old) females with early-onset HTN
- Associated conditions: Marfan and Ehlers-Danlos syndromes, tuberous sclerosis, cystic medial necrosis, coarctation of aorta, Alport syndrome, renal agenesis or dysgenesis, α1-antitrypsin deficiency, medullary sponge kidney, pheochromocytoma, infantile myofibromatosis, ergotamine preparation, methysergide, cigarette smoking, collagen III glomerulopathy, atherosclerotic renovascular disease
- FMD typically occurs in the middle or distal portions of renal artery or branch vessels and may present with aneurysms, occlusion, dissection, arteriovenous fistulas, or thrombosis. Lesions are characterized by disruptions of vascular wall components with abnormal collagen deposition in bands with or without disruption of elastic membrane.

FMD types

- Medial (85%-100%) > intimal (<10%) > adventitial (<1%)
- Medial and perimedial fibroplasia classically have "string of beads" appearance. Medial *hyperplasia* may only present as smooth stenosis of artery.
- Intimal and adventitial fibroplasia present as smooth stenotic segments or diffuse attenuation of vessel lumen.

Natural history

- Progression of disease slows down with age.
- Rarely causes ischemic kidney failure, but associated thrombosis or dissection of affected renal vessel may lead to renal infarction.

Management of FMD with HTN

- Percutaneous transluminal renal angioplasty (PTRA) versus surgical revascularization
  - Revascularization should be strongly considered in FMD.
  - PTRA:

    - Higher chance of BP lowering following PTRA in younger patients or those with lower pre-PTRA BP, shorter duration of HTN, and positive captopril test
    - If restenosis occurs, repeat PTRA may be performed as needed.
  - Surgical revascularization: If aneurysmal dilations >1.5 cm in diameter; covered stent grafts may also be used in renal artery aneurysms.
- Preferred antihypertensive agents include ACEi or ARB.
- Imaging of other vascular beds, for example, internal carotids and vertebral arteries, should be considered in individuals with FMD because other vessels may also be affected.

Acute Intermittent Porphyria (AIP)

Rare autosomal dominant disorder with deficiency of porphobilinogen deaminase, the third enzyme in heme biosynthesis. AIP is associated with the accumulation of porphobilinogens (PBGs) and delta-aminolevulinic acid (ALA) and increased urinary excretion of ALA, PBG, and porphyrins.

Clinical manifestations

- More commonly affects women from second to fourth decades of life.
- Most affected individuals are asymptomatic.
- AIP may be activated following puberty during menstrual cycles (progesterone) or use of drugs such as rifampin, progestins, anticonvulsants, barbiturates.
- Symptoms may include intermittent severe colicky abdominal pain, constipation (may be misdiagnosed as intestinal obstruction), dystonic bladder with urinary retention/incontinence, reddish brown urine when exposed to sunlight, autonomic dysfunction with increased circulating catecholamine levels resulting in HTN, tachycardia, sweating, restlessness and tremors,

peripheral neuropathy, proximal muscle weakness, neuropsychiatric disorders (hallucinations, delirium, flaccid paralysis, seizures), syndrome of inappropriate antidiuretic hormone (SIADH) with hyponatremia. Skin rash is not a typical manifestation compared to other forms of porphyria.

- Attacks may be brought on by infections, hormonal or dietary changes/starvation, drugs, severe illness, infections, surgery, smoking, alcohol.

Diagnosis: elevated urinary PBGs (urine spot test)

Management

- Mild attacks: high-dose oral glucose (400 g/d) or IV dextrose 10% solution
- Severe attacks, severe neurologic symptoms: hematin (hemin) 4 mg/kg/d for 4 days
- Pain control with narcotics as needed
- Laxatives, softeners for constipation, particularly if narcotics are used
- Gabapentin for seizures

Endocrinologic Disorders

Endocrinologic disorders associated with HTN may be categorized based on specific endocrine glands, starting from pituitary (acromegaly, Cushing disease) → thyroid (hypothyroidism, hyperthyroidism) → parathyroid (hyperparathyroidism) → adrenal glands (pheochromocytoma, adrenal hyperplasia/tumor, congenital hyperplasia).

Pituitary

Acromegaly

Acromegaly is caused by the hypersecretion of growth hormone (GH) by pituitary tumor or tumors other than pituitary (eg,

hypothalamic or nonendocrine tumors such as breast, pancreatic, or bronchial malignancies). Excess GH stimulates hepatic secretion of insulin-like growth factor-1 (IGF-1), which is responsible for most clinical manifestations of acromegaly.

Clinical manifestations: skull, hands, feet enlargement, excessive sweating, carpal tunnel syndrome, sexual dysfunction, DM, thyromegaly, thyrotoxicosis, headaches, visual field defects, colon polyps

Pathogenesis of HTN

- Sodium retention with inappropriately normal to only minimally low renin and aldosterone levels and normal atrial natriuretic peptide
- Others: GH-induced vascular hypertrophy with decreased vascular compliance, increased SNS, associated hyperthyroidism

Diagnosis of acromegaly

- Elevated plasma IGF-1 confirms the diagnosis.
- If IGF-1 level is indeterminate, measure GH following an oral glucose challenge. Unsuppressed GH level following glucose challenge confirms the diagnosis.
- Imaging studies: Magnetic resonance imaging (MRI) of pituitary fossa; if extrapituitary source is suspected, obtain chest and abdominal computed tomography (CT).

Management options

- Tumor specific:
  - Transsphenoidal adenomectomy is the treatment of choice if possible.
  - Medical therapy: somatostatin analogs (eg, octreotide, lanreotide), GH receptor antagonist (pegvisomant); for mild disease, dopamine agonist cabergoline
  - Tumor radiation may also be considered in some cases of failed medical therapy.
- HTN: diuretics as primary agent, addition of others as needed

Cushing disease (and Cushing syndrome)

Cushing disease refers to pituitary adenoma producing excess adrenocorticotropic hormone (ACTH). Cushing syndrome refers to conditions where excess ACTH is produced by sources other than pituitary, for example, adrenal tumors, bronchogenic carcinoma.

Clinical manifestations

- Excess cortisol state is associated with HTN, DM, coagulopathy, CVDs, infections, osteoporosis, and fractures.
- Patients may present with central weight gain, round face, fat deposition at neck base, abdominal striae, easy bruising, generalized muscle weakness.

Pathogenesis of HTN

- Increased mineralocorticoid activity from the excess cortisol and/or concurrent mineralocorticoid production
- Increased cardiac output and peripheral vascular resistance
- Increased sensitivity to catecholamines, Ang II, and β-adrenergic stimulation

Diagnosis

- The Endocrine Society recommends using at least two of three different screening tests: 24-hour urine free cortisol excretion, late night/bedtime salivary cortisol levels, and the 1 mg overnight dexamethasone suppression test (DST) or, alternatively, the 2-mg 2-day DST.
- Once hypercortisolism has been established, obtain ACTH level to determine source, that is, ACTH dependent (pituitary, ectopic) or ACTH independent (primary adrenal). Consult endocrinology for interpretation of results and further testing.

Management options

- Resection (or second-line pituitary irradiation) of ACTH-producing tumors
- Medical therapy per endocrinology: cabergoline, somatostatin analog (eg, pasireotide), chemotherapy (eg, mitotane)
- Bilateral adrenalectomy

- HTN: Consider potassium-sparing diuretics, specifically MRA.

Thyroid

Hypothyroidism

- Underlying mechanisms of HTN are thought to be due to reduced cardiac contractility and output with resultant increased sodium retention.
- Hemodynamic alterations associated with hypothyroidism
  - Bradycardia
  - Mild HTN with a narrow pulse pressure due to reduced cardiac contractility and output
  - Elevated DBP is seen in ~30% of patients with overt hypothyroidism.

Hyperthyroidism

- Underlying mechanisms of HTN are thought to be due to increased cardiac output, heart rate, and myocardium contractility, volume expansion, and increased RAAS but not SNS activity.
- HTN may be associated with normal or high pulse pressure.

Parathyroid

Hyperparathyroidism-associated HTN is thought to be due to increased peripheral vascular resistance, presumably due to hypercalcemia, although the exact mechanism is unclear.

Adrenals

Pheochromocytoma and paragangliomas (PPGL)

- 90% arise from adrenals and 10% are extra-adrenal. The latter are termed paragangliomas (PGLs).

- Common hormones produced include NE, epinephrine, and dopamine.
- Malignant disease or large tumor mass may have very high dopamine levels.

Sporadic disease

- Often focal, unilateral involvement
- Up to 14% have somatic mutations.

Familial PPGL associated with HTN

- Familial disease typically presents as multifocal, bilateral, or extra-adrenal disease in younger patients, that is, <50 years old, and may be associated with germline mutations, which are mostly autosomal dominant.
- *RET* gene:
  - Multiple endocrine neoplasia type 2a: medullary thyroid carcinoma, hyperparathyroidism, cutaneous lichen amyloid; type 2b: medullary thyroid carcinoma, multiple neuromas, marfanoid habitus
  - Predominant epinephrine secretion
- von Hippel-Lindau gene: von Hippel-Lindau syndrome
  - Syndrome with retinal and central nervous system (CNS) hemangioblastomas, renal cell carcinoma, pancreatic, endolymphatic sac, epididymal tumors
  - Predominant noradrenergic (ie, NE) secretion
- Neurofibromatosis type 1 gene (aka von Recklinghausen disease):
  - Clinical characteristics: neurofibromas, café-au-lait spots
  - Predominant epinephrine secretion

Common clinical manifestations of PPGL

- BP manifestations
  - Paroxysmal or sustained HTN or orthostatic hypotension
  - NE activates α-adrenergic receptors, which can lead to vasoconstriction, volume contraction, and HTN. Patients with NE-secreting PPGL tend to present with sustained HTN.

    - Epinephrine also activates β2-adrenergic receptors, which can cause vasodilation and postural hypotension. Patients with epinephrine-secreting PPGL more commonly present with paroxysmal HTN and orthostatic hypotension.
- Others: headaches, diaphoresis, palpitations, anxiety, chest/abdominal pain, nausea/vomiting, dyspnea, pallor, catecholamine-associated cardiomyopathy (Takotsubo syndrome)
- Symptoms of PPGL can be triggered by stress, exercise, delivery, anesthesia, tumor manipulation, or medications such as β-blockers, antidepressants, metoclopramide.

Diagnosis

- Plasma free metanephrines (metanephrines and normetanephrines) greater than 4- to 5-fold of upper limit of normal suggest the presence of PPGL is highly probable (sensitivity of 97% and specificity of 93%). Plasma fractionated catecholamine (epinephrine, NE, and dopamine) testing is less sensitive but levels >2 times upper limit of normal range are diagnostic. See **Appendix A5.2** for differences between the two tests.
- Acute illnesses and medications may increase levels of metanephrines and catecholamines (tricyclic antidepressants, antipsychotic agents, serotonin reuptake or NE reuptake inhibitors, and levodopa).
    - If screening plasma fractionated metanephrines is >4 to 5 times upper normal limit, localize tumor with either contrast-enhanced CT or T2-weighted MRI of entire retroperitoneum.
    - If levels are in the intermediate range (eg, elevated but not >4-5 times above upper normal limit), repeat testing, obtain both plasma free and urinary fractionated metanephrines (sensitivity 86%-97%, specificity 60%-95%). Consider clonidine suppression test (0.3 mg clonidine) if repeat testing is equivocal. Clonidine is an α2-adrenoreceptor agonist that inhibits neuronal NE release in patients without PPGL, but not in those with autonomous secretion of catecholamines by

PPGL. Positive test: failure to reduce plasma catecholamines to >50% from baseline at 3 hours post clonidine

Imaging studies

- MRI or CT: abdomen/pelvis if no family history; neck to pelvis if family history or suspicion for genetic disease
- Functional testing may be used to evaluate for metastatic disease or identification of multiple chromaffin tumors.
- Functional testing may include: ^{123}Iodine-labeled metaiodobenzylguanidine (MIBG) scan or positron emission tomography (PET)-CT scan with ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-octreotate (DOTATATE) or ^{18}F-labeled L-dihydroxyphenylalanine (L-DOPA).

Management

- BP control:
  - α-Adrenergic blockers and/or catecholamine synthesis inhibitor metyrosine
    - Initiate an α-adrenergic blocker 7 to 14 days prior to surgery.
    - First-line therapy: nonselective α-blocker phenoxybenzamine (PBZ; start at 10 mg po bid, titrate up to 30 mg tid to achieve low normal for age) or
    - Alternative: selective α-blocker (doxazosin [DOX] 1 mg qd, titrate up to 10 mg bid)

FYI

PBZ is an irreversible noncompetitive inhibitor of α1 and α2 receptors, while DOX is a competitive inhibitor of α1 receptor. Large surges of catecholamine release during surgical manipulation of the pheochromocytoma may overwhelm the competitive inhibitory effect of DOX. A randomized, multicenter, open-label clinical trial comparing the effect of PBZ and DOX on intraoperative hemodynamic instability (Phenoxybenzamine vs Doxazosin in Pheochromocytoma Patients [PRESCRIPT]) involving 134 patients with nonmetastatic PPGL or sympathetic PGL revealed that treatment with PBZ or DOX starting 2 to 3 weeks before surgery resulted in (1) no difference in the duration of BP outside the target range during PPGL resection; (2) PBZ was

more effective in preventing intraoperative hemodynamic instability. However, whether this translated to better clinical outcome could not be established.

        - Liberalize sodium and fluid intake while on α-blockers if no history of HF.
    - Add β-blockers to control tachycardia or arrhythmias after BP has been controlled with α-adrenergic inhibition.
    - Consider dihydropyridine CCB as add-on therapy for BP control.
- Surgical removal
    - Preoperative preparation: BP control as above.
    - Intraoperative BP management options: IV phentolamine (nonselective, reversible, competitive α-antagonist), sodium nitroprusside, and magnesium sulfate
    - Postoperative management: Monitor for hypoglycemia and hypotension.
    - Long-term management
        - BP control if persistent HTN
        - If malignant PPGL, use both α- and β-adrenergic blockers as needed for symptoms, radiation therapy for bone metastatic disease, and chemotherapy (cyclophosphamide, vincristine, and dacarbazine).
    - Follow-up: Biochemical profile (plasma free or urine fractionated metanephrines) annually and imaging study every 1 to 2 years depending on risks. High-risk patients including young patients and those with genetic mutation, large tumor, and/or PGLs should be offered life-long follow-up. For interested readers, review the European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a pheochromocytoma or PGL.

Adrenal incidentaloma/hyperplasia/adenoma/carcinoma

- The prevalence of PA increases with increasing HTN severity. PA prevalence has been reported to range from 15.7% to 21.6% to

22.0% among patients with stage 1, stage 2, and resistant HTN, respectively.

- PA is considered the most common modifiable form of secondary HTN.

Clinical manifestations

- Classic triad of HTN, hypokalemia, and metabolic alkalosis may be present. However, hypokalemia is prevalent in only approximately 50% of patients with aldosterone-producing adenomas and 25% in bilateral adrenal hyperplasia. This is the rationale for PA screening in patients with severe HTN regardless of serum potassium level.
- Hypokalemia and increased plasma aldosterone level may occur over time in patients with evolving PA. New-onset or worsening of hypokalemia should prompt reevaluation for PA.
- Increased risk of cardiac and cerebrovascular events and target organ damage involving kidneys (glomerular hyperfiltration, proteinuria, CKD) and heart (eg, coronary artery disease, HF, LVH, atrial fibrillation) may be observed in patients with PA relative to those with essential HTN. The increased risk is thought to be related to the elevated aldosterone level per se independent of BP control.

Diagnosis of PA involves screening, confirmatory testing, imaging, followed by adrenal vein sampling if surgery is an option. See **Table 5.2**.

Table 5.2 Evaluation of primary aldosteronism based on the Endocrine Society Clinical Practice Guideline

Diagnostic Testing for Primary Aldosteronism	
Criteria for screening	• BP >150/100 mm Hg on three separate BP measured on different days. • Difficult-to-treat HTN • HTN and any one of the following: spontaneous or diuretic induced hypokalemia, adrenal incidentaloma, sleep apnea,

Diagnostic Testing for Primary Aldosteronism

	family history of early onset HTN or CVA at age <40 years old, first-degree relatives with PA
Screening tests	• [a]PAC (ng/dL) to PRA ratio (ng/mL/h), aka aldosterone-to-renin ratio (ARR): • In the setting of undetectable PRA, PAC >20 ng/dL, and spontaneous or diuretic induced hypokalemia, no confirmatory testing is needed. → Proceed to adrenal CT or MRI. • ARR >20 ng/dL/ng/mL/h → Proceed to confirmatory testing.
Confirmatory testing options (perform one or more)	• [b]Oral salt loading: ↑Na^+ intake to >200 mmol/d × 3 d and supplement K^+ to normalize serum K^+ level. • Positive test: 24-h urine aldosterone measured on the morning of day 3 to morning of day 4 is >12-14 µg. Urine Na^+ should be >200 mmol to assure compliance with Na^+ load. • [b]Intravenous salt loading done at 8:00 to 9:30 AM: Infuse 2 L normal saline over 4 h (recumbent 1 h prior or sitting for 30 min prior to and during infusion). • [c]Positive test (recumbent): PAC >5-10 ng/dL (reference: <5 ng/dL) • [c]Positive test (sitting): PAC >6 ng/dL • [b]Fludrocortisone-suppression test: Administer fludrocortisone acetate 0.1 mg po q6h with high Na^+ diet (3 mmol/kg/d) × 4 d and supplement K^+ to normalize serum K^+ level. • [c]Positive test: Day 4, 10 AM, in sitting position, PAC >6 ng/dL and PRA <1.0 ng/mL/h • [d]Captopril challenge: Administer captopril 25-50 mg orally after sitting or standing for ≥1 h. • Positive test: After 1-2 h, PAC decreases ≤30% or ARR >200 pg/mL/ng/mL/h.
Adrenal CT or MRI	• Assess for unilateral vs bilateral disease
Adrenal vein sampling (AVS)	• AVS may be done prior to surgery to confirm affected side. • Lateralization index >8 confirms affected side and predicts improved BP following surgical removal.

Diagnostic Testing for Primary Aldosteronism

	• AVS is not needed in young patients with unilateral adenoma by imaging study and marked PA.
Genetic testing	• Consider if PA onset at <20 years old or with family history of PA or stroke at <40 years old.

Abbreviations: BP, blood pressure; CT, computed tomography; CVA, cerebrovascular accident; HTN, hypertension; MRI, magnetic resonance imaging; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

For interested readers, refer to Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016:101(5):1889-1916 for a full discussion of the evaluation of primary aldosteronism.

[a]There is a lack of uniformity in diagnostic protocols and assay methods for measuring aldosterone-to-renin ratios. Clinicians must review institutional units for measured PAC and PRA because these will affect the ratio cutoff values. Additionally, some centers may use plasma renin concentration rather than plasma renin activity, which also give rise to different ratio cutoff values.

[b]Test should not be done in patients with heart failure, severe uncontrolled hypertension, severely reduced kidney function, cardiac arrhythmias, or severe hypokalemia.

[c]Plasma cortisol concentration following testing should be lower than the basal value at 7 am to exclude a confounding ACTH effect.

[d]Diagnostic sensitivity may not be optimal.

Screening for PA

- Per the ES Clinical Practice Guidelines, screening plasma aldosterone concentration to plasma renin activity (PRA) ratio, known as aldosterone to renin ratio or ARR, is recommended for patients with HTN and any one of the following:
  - Three sustained BP measurements >150/100 mm Hg obtained on different days
  - Difficult-to-treat HTN (BP uncontrolled on 3 appropriate antihypertensive agents from different classes at maximally tolerated doses, one of which is a diuretic, or BP controlled on 4 agents, one of which is a diuretic)
  - Spontaneous or diuretic-induced hypokalemia
  - Adrenal incidentaloma
  - Sleep apnea

  - Family history of early-onset HTN or cerebrovascular accident at age <40 years
  - All first-degree relatives of patients with PA
- Interpretation of ARR
  - For cases of undetectable PRA or ARR >20 ng/dL/ng/mL/h in individuals with spontaneous or diuretic-induced hypokalemia, proceed directly to imaging study to assess for unilateral versus bilateral disease.
  - For all other individuals with ARR >20 ng/dL/ng/mL/h, proceed to confirmatory testing.

Confirmatory testing options

In individuals with normal adrenal function, the following testing options should suppress aldosterone synthesis, reduce aldosterone concentrations, and increase PRA or renin concentration. In individuals with PA, aldosterone synthesis is not suppressible and corresponding changes in PRA or renin do not occur. See **Table 5.2**.

- Oral or IV salt load
- Fludrocortisone suppression test
- Captopril challenge

FYI

During diagnostic testing for PA, avoid medications that can affect ARR if clinically safe.

- Withdraw 4 weeks prior to testing: diuretics, MRA
- Withdraw 2 weeks prior to testing: β-blockers, clonidine, methyldopa, NSAIDs, ACEi, ARB, dihydropyridine CCB
- Acceptable drugs to use during testing period: non-dihydropyridine long-acting CCBs (verapamil, diltiazem), hydralazine, α1-adrenergic receptor blockers (eg, prazosin, DOX, terazosin)
- If drug withdrawal along with substitution with "acceptable drugs" listed is not safe, interpret obtained ARR accordingly. See Funder et al (2016).

In cases where plasma renin concentration instead of plasma renin activity is measured, an aldosterone to renin concentration ratio (ARC) is used. Cutoff level for ARC has been suggested to range between 26.35 and 59.66 ((ng/L)/(ng/L)). Note that with the use of direct renin inhibitors (DRIs), PRA is decreased but the actual

renin concentration is increased. The use of ARR in patients receiving DRI would thus yield falsely positive results while ARC would yield falsely negative results.

Imaging studies

- CT/MRI with adrenal cuts can be done following confirmatory testing to assess unilateral versus bilateral disease and possibility of malignant lesions.
- Adrenal carcinoma is more likely with increasing size: 2% of masses up to 4 cm, 6% of masses from 4 to 6 cm, 25% of masses >6 cm are malignant.

Adrenal venous sampling (AVS) for lateralization of aldosterone levels

- AVS is recommended to confirm the side of the hyperfunctioning gland prior to removal.
  - Step 1: Confirm successful canalization of adrenal vein: Cortisol levels at both the IVC and the adrenal vein are measured. An adrenal vein to IVC cortisol ratio, known as selectivity index (SI), of >3 suggests successful adrenal vein catheterization. Some experts suggest adding a continuous infusion of cosyntropin at 50 µg/h started 30 minutes prior to AVS to improve sensitivity and specificity. If cosyntropin is added, a ratio of >5 is used as the cutoff as an indication for successful canalization of the adrenal vein.
  - Step 2: Obtain aldosterone levels from both adrenal veins: Since the aldosterone level may be diluted when it is collected further away from the adrenal gland, an aldosterone to cortisol ratio (A:C ratio) is used to correct for this effect. An A:C ratio is obtained and calculated for each side.
  - Step 3: Calculate a lateralization index (LI): LI is defined as A:C ratio of suspected PA side divided by the A:C ratio of the contralateral side. An LI >4 is suggestive of unilateral disease. An LI <3 is suggestive of bilateral disease. An LI >8 has been shown to be significantly associated with BP improvement following adrenalectomy.

- Note: Prior to calculating LI, the SI from each side should be greater than 3:1 (if no cosyntropin is infused) or at least 5:1 (if cosyntropin is infused) for accurate interpretation.

- Young patients <35 years of age with spontaneous hypokalemia, marked aldosterone excess, and a unilateral adenoma on CT imaging do not need AVS for lateralization.

Management of hyperaldosteronism

- Unilateral PA: adrenalectomy if surgical candidate
- Nonsurgical unilateral PA or bilateral PA
  - In patients with PA, the use of MRA (eg, spironolactone, eplerenone) to achieve PRA level ≥1.0 ng/mL/h (beyond BP and potassium control) has been shown to improve CV outcomes to levels similar to those with essential HTN.
  - Novel therapy:
    - Selective aldosterone synthase activity blocker (Baxdrostat) has been shown to significantly reduce BP while reducing aldosterone levels in patients with resistant HTN (phase 2 clinical trial; Freeman et al 2023). Reduced aldosterone levels may confer better long-term end-organ protection compared with MRA. Unlike Baxdrostat, MRAs increase plasma aldosterone levels. Lorundrostat is another aldosterone synthase inhibitor that has been shown to reduce BP.
    - Interfering RNA: Zilebesiran is a long-acting interfering RNA that inhibits hepatic angiotensinogen synthesis and has been shown to reduce 24 hours SBP at 12 weeks by 13 to 16 mm Hg compared with placebo in a trial involving 84 patients with HTN.
  - Dietary sodium restriction to <50 mmol/d has been shown to effectively reduce ARR in patients with PA.
- Surgical versus medical intervention:
  - Higher CV events, mortality, and atrial fibrillation may be associated with medical therapy compared with surgical

intervention in longitudinal studies. It is possible that patient selection bias may have contributed to findings.

- Worse CV outcomes appear to correlate with persistently suppressed PRA <1 µL/L/h rather than degree of BP control. MRA titration to achieve PRA >1 µL/L/h rather than to target BP has been suggested.

Familial hyperaldosteronism (FH)

Genetic testing: Patients with disease onset <20 years of age and patients with a family history of PA or stroke at age <40 years should undergo testing for glucocorticoid remediable aldosteronism (GRA; FH type 1) and germline mutations in *KCNJ5*.

FH type I: aka GRA or dexamethasone-suppressible hyperaldosteronism

- FH results from an uneven crossover of genes during meiosis that results in the formation of a chimeric gene, where ACTH, instead of Ang II, regulates aldosterone synthase activity in the cortisol-producing zona fasciculata of the adrenal cortex. As such, aldosterone synthesis occurs in response to ACTH, independent of Ang II. Inhibition of ACTH by glucocorticoid inhibits aldosterone synthase activity.
- FH type I (GRA) may be treated with the lowest dose of dexamethasone.

FH types II to IV: See **Appendix A5.3** for other types of FH where mutations of various genes can lead to activation of aldosterone synthase.

HTN, hypokalemia, and metabolic alkalosis triad

Conditions other than adrenal hyperplasia/adenoma that present with the clinical triad of HTN, hypokalemia, and metabolic alkalosis include:

Aldosterone dependent:

- Primary aldosteronism

- Secondary hyperaldosteronism, for example, hyperreninemic hyperaldosteronism: renal artery stenosis, renin-secreting tumors
- Glucocorticoid remediable aldosteronism

Cortisol dependent:

- Excess cortisol (eg, Cushing syndrome/disease): Cortisol has mineralocorticoid activity.
- Reduced metabolism of cortisol:
  - Apparent mineralocorticoid excess syndrome: reduced conversion of cortisol to inactive cortisone by the enzyme 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2) due to loss-of-function mutation of 11β-HSD2
  - Licorice ingestion: Glycyrrhetinic acid from licorice inhibits 11β-HSD2.

Non-aldosterone, non-cortisol dependent:

- Congenital adrenal hyperplasia: accumulation of steroid intermediates with mineralocorticoid activity, for example, deoxycorticosterone
- Geller syndrome: gain-of-function mutation of mineralocorticoid receptor
- Liddle syndrome: gain-of-function mutation of ENaC; treatment: amiloride

Review **Hypokalemia** in **Chapter 2: Acid-Base and Potassium Disorders** for mechanisms of disease and management of these conditions.

HTN, hyperkalemia, and metabolic acidosis triad

Conditions that can present with the triad of HTN, hyperkalemia, and metabolic acidosis include Gordon syndrome, aka pseudohypoaldosteronism type 2 and the use of calcineurin inhibitors (CNIs; tacrolimus, CSA). Treatment for these conditions is thiazide diuretic. See **Chapter 2: Acid-Base and Potassium Disorders** for pathogenesis of Gordon syndrome.

CNI-induced HTN associated with hyperkalemia and metabolic acidosis

- CNI-induced HTN is thought to be multifactorial and includes afferent arterial vasoconstriction leading to reduced GFR and thus sodium retention, reduction of endothelium-derived relaxing factor and nitric oxide activity, increased production of the potent vasoconstrictor endothelin-1, activation of RAAS, and increased expression of the phosphorylated (active) form of the thiazide-sensitive NaCl cotransporter (NCC).
- Clinical manifestations include renal sodium retention (HTN) and potassium retention (hyperkalemia), renal tubular acidosis, hypomagnesemia, and/or hypercalciuria. Treatment includes dietary sodium restriction and thiazide diuretics.

Miscellaneous

- Klotho gene deficiency has been suggested to play a role in HTN associated with aging. The decline in Klotho expression is associated with upregulation of adrenal *CYP11B2* expression (gene encoding aldosterone synthase), a key rate-limiting enzyme for aldosterone synthesis.
- Shorter sleep duration and frequent interrupted sleep may be at increased risk for HTN.
- Coarse particulate from air pollution has been suggested to contribute to HTN via interaction with pulmonary receptors and associated heightened SNS activity.

END-ORGAN DAMAGE OF HTN

Kidney Injury

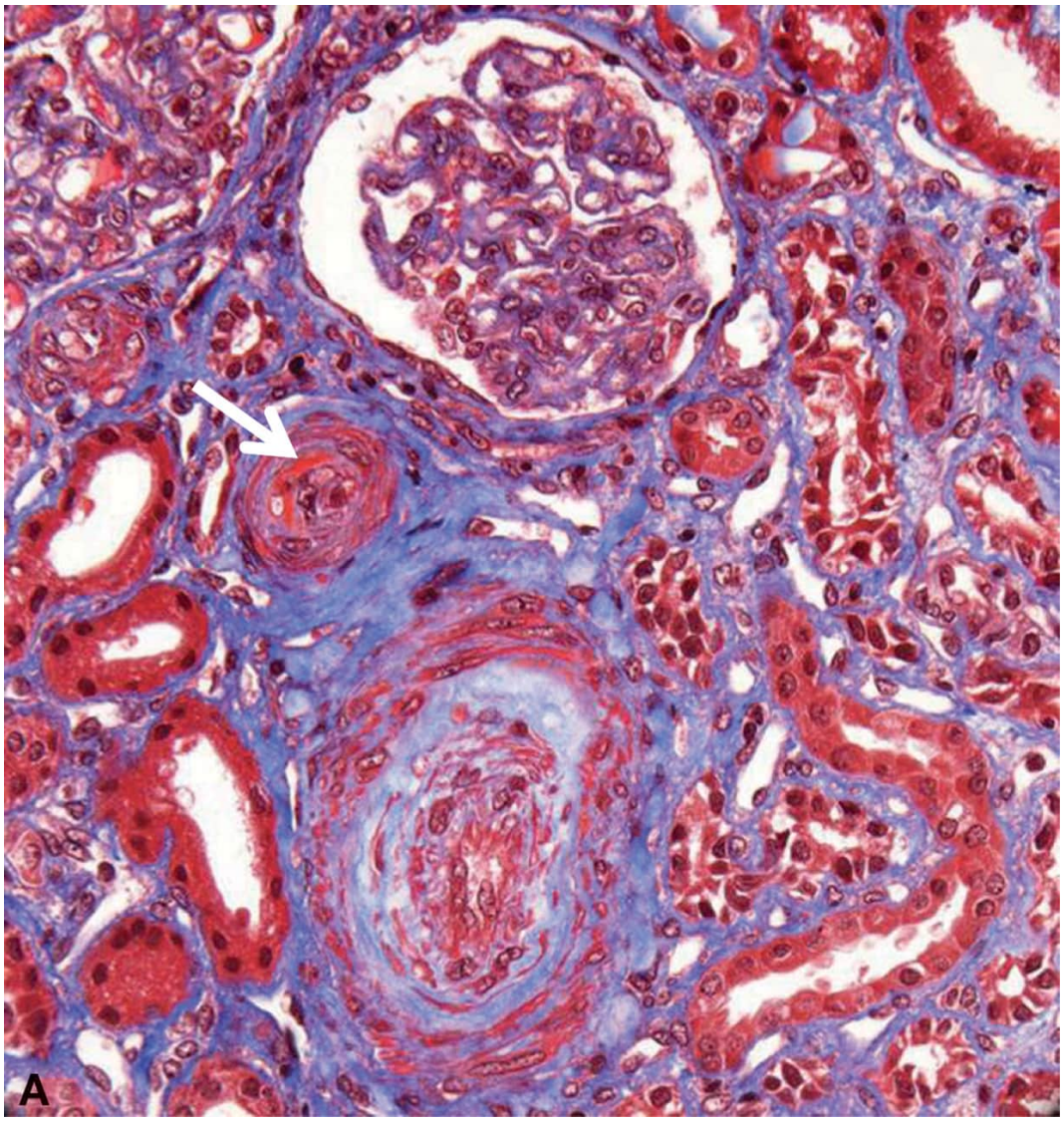
Acute hypertensive nephrosclerosis associated with hypertensive emergencies

Clinical manifestations: hematuria, AKI

Pathogenesis: direct endothelial damage, ischemic injury, microangiopathic hemolytic anemia causing obstruction of

interlobular arteries

Histopathology (**Figure 5.3**): Fibrinoid necrosis of arterioles and small arteries (pink, amorphous fibrinoid materials within the intima and occasionally media due to necrosis) and swollen endothelial cells with luminal narrowing, with or without luminal thrombosis. Small arteries also may have wide pale edematous (mucoid) myointimal thickening. In malignant HTN, glomeruli often are not thrombosed. In subacute injury, the walls of arterioles and small arteries will have "onion skinning," which is hyperplasia of the muscular wall with thickened concentric smooth muscle cell layers and thickened, duplicated basement membrane causing narrowed lumens. Acute and subacute changes may be coincidental.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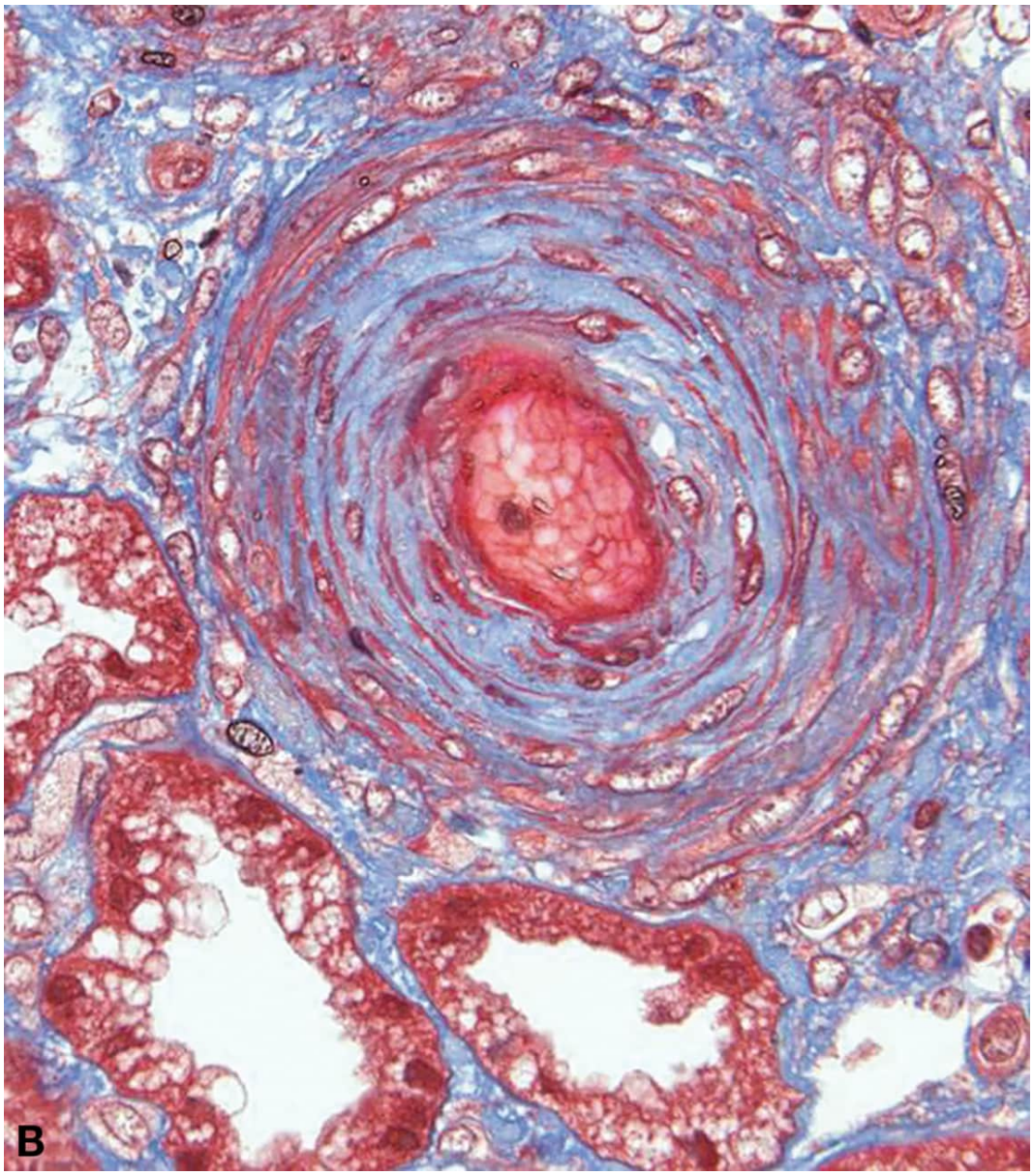


FIGURE 5.3 Accelerated/malignant hypertension/hypertensive renal emergency. A. Small artery and arteriole showing endothelial cell swelling and severe luminal narrowing. The artery has mucoid intimal thickening, the arteriole has fibrin in the wall (arrow), and the glomerulus has early ischemic capillary wall corrugation (Masson's trichrome ×250). B. Small artery with subacute "onion skin" pattern of myointimal thickening with concomitant active luminal thrombosis (Masson's trichrome ×400).

Chronic hypertensive nephropathy

Clinical manifestations

- Slowly progressive kidney injury with relatively bland urine, mild albuminuria
- ESKD due solely to HTN is uncommon due to the relative preservation of glomerular injury until advanced stage except for genetically susceptible subpopulation such as African Americans or those who suffer from frequent hypertensive emergency episodes and associated acute hypertensive nephrosclerosis. The relative glomerular sparing is consistent with minimal albuminuria associated with chronic hypertensive nephropathy.

Histopathology: Thickening and fibrosis/sclerosis of renal resistance arteries, thickening of arteriolar walls with hyalinosis (insudates), and slowly progressive thickening and corrugation of glomerular capillaries. Ischemic glomerular injury with deflation and global obliteration occurs slowly over decades.

CV Complications

Acute cardiac complications associated with hypertensive emergencies

- Acute coronary syndrome, acute myocardial infarction
- Acute left ventricular dysfunction, acute HF
- Acute aortic dissection

Chronic cardiac complications

- In older patients, SBP and pulse pressure are better determinants of CVD risk than DBP. (Recall DBP decreases after age 50.)
- Chronic cardiac complications: LVH that increases the risk of myocardial infarction, HF, ventricular arrhythmias, sudden cardiac death, diastolic dysfunction

Cerebrovascular Complications

Acute complications: ischemic stroke, intracerebral or subarachnoid hemorrhage

Chronic complications: ischemic stroke, vascular dementia, lacunar infarctions, microhemorrhages, focal or diffuse white matter lesions (early hypertensive microangiopathic complications)

Ophthalmologic Complications

- Grade I retinopathy: arteriolar narrowing (related to vasospasm)
- Grade II retinopathy: arteriovenous nicking
- Grade III retinopathy: cottonwool spots, hard exudates, microaneurysms, hemorrhages (dot-shaped or flames)
- Grade IV: all of the above plus papilledema
- The presence of papilledema defines hypertensive emergency and requires rapid BP lowering.

PHARMACOLOGIC THERAPY FOR HTN

Initiating Pharmacologic Therapy

Combination versus monotherapy

For drug-naïve patients with SBP >20/10 mm Hg above goal, two-drug therapy should be initiated.

First-line therapy

First-line antihypertensive drugs include an ACEi or ARB, dihydropyridine CCB, and thiazide diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) did not show any difference in coronary heart disease or nonfatal myocardial infarction and stroke among CCB, ACEi, or thiazide diuretic. Conversion of a thiazide diuretic to loop diuretic may be done for those with concurrent volume overload.

Compelling indications

Drug selection may depend on underlying conditions, for example, ACEi/ARB for systolic HF, post-myocardial infarction, α-blockers for benign prostate hypertrophy, β-blockers for essential tremors,

hyperthyroidism, migraine, atrial fibrillation/flutter with rapid ventricular rates, angina, MRA for hyperaldosteronism, thiazide diuretics for osteoporosis, etc. Note, however, α-blockers, β-blockers, and MRA are not first-line agents, but may be used as first-line if clinically indicated.

Special Considerations in the Selection of Pharmacologic Therapy for HTN

ACEi or ARB should be considered for the following:

- Patients without diabetes with HTN and albuminuria ≥30 mg/d
- Patients with and without diabetes with albuminuria ≥300 mg/d
- Patients with HTN and CKD (including African Americans)
- The use of ACEi and ARB is safe in patients at risk for or infected with COVID-19.

Thiazide diuretics

Clinically available thiazide and thiazide-like diuretics

- Thiazide diuretic: hydrochlorothiazide (HCTZ)
- Thiazide-like diuretics: chlorthalidone (CTDN) and indapamide (INDAP)
- The longer duration of action of CTDN and INDAP compared with HCTZ may confer better nighttime BP control: HCTZ (<24 hours), CTDN (24-72 hours), INDAP (24+ hours and 32+ hours for immediate-release and sustained release forms, respectively)

The use of thiazides in individuals with CKD

CTDN has been shown to remain effective in reducing SBP by 19 to 20 mm Hg even in patients with advanced CKD G4. Continuation of thiazide diuretic rather than switching to loop diuretic may be appropriate in a stable patient if volume overload is not a concern. Loop diuretic switch is reasonable in the case of volume overload.

CVD protection: CTDN has been shown to confer improved CVD outcomes compared with HCTZ in multiple large studies. Of note, however, a 2022 VA study involving veterans with mean age of 72

years over median follow-up of 2.4 years revealed no difference in CV outcomes between HCTZ and CTDN. See **Appendix A5.4.**

Protection against fracture: Thiazide and thiazide-like diuretics have been shown to confer long-term protection against fractures compared with other antihypertensive agents. This is presumably via the hypocalciuric effect of thiazides.

MRAs (spironolactone, eplerenone, finerenone)

Indications:

- Recommended to be used concurrently with thiazide diuretics to offset hypokalemia
- Recommended to be added in resistant HTN, for eg, spironolactone 25 to 50 mg daily. See **Appendix A5.5**.
- Finerenone has been shown to effectively reduce BP among patients with resistant HTN and moderate to advanced CKD, although at a lower extent compared with spironolactone (−7.1 mm Hg vs −10.8 mm Hg respectively). The incidence of developing serum [K^+] ≥5.5 mmol/L is much lower with finerenone compared with that of spironolactone (12% vs 64%). See **Appendix A5.6**.

Special notes:

- MRA confers additional benefits in CV outcomes in patients with New York Heart Association (NYHA) class III-IV HF or decreased left ventricular ejection fraction after a myocardial infarction.
- BP lowering effect has been shown to be more pronounced in patients with suppressed PRA. Suppressed PRA is consistent with high aldosterone levels. Nonetheless, MRA may lower BP regardless of serum aldosterone levels.
- MRA may reduce BP even among patients receiving hemodialysis.

Adverse effects: hyperkalemia, metabolic acidosis, feminization effects with spironolactone

Direct renin inhibitor

The DRI aliskiren reduces BP comparably to ACEi and ARB. Combination therapy of DRI + ACEi or ARB provides minimal added benefit if any compared with lone ACEi/ARB therapy at the expense of greater serious side effects. See **Appendix A5.7**.

Obesity and antihypertensive therapy

ACEi/ARB may be considered as first line

- There is evidence for activated RAAS in obese patients. Mechanisms are thought to be due to increased SNS activity leading to activated RAAS and/or excess visceral/retroperitoneal fat compression of kidneys leading to reduced renal blood flow, thereby activating RAAS.
- ACEi and ARB have also been shown to confer improved insulin sensitivity and renoprotective effects in patients with DM.

β-Blockers

- Theoretically beneficial given activated SNS; However, these agents may have adverse effects on lipid and glucose metabolisms and weight gain.
- May consider β-blockers if concurrent cardiac indications, in which case, third-generation agents such as carvedilol and nebivolol are preferred.

Thiazides

Beneficial for volume overloaded state, but need to consider adverse metabolic effects

Dihydropyridine CCBs

CCBs have neutral effect on glucose metabolism and weight gain; use as second-line agent.

Considerations for BP management in African Americans

- Use of two-drug combination therapy is recommended in most African Americans.
- For those without HF or CKD who do not meet criteria for two-drug therapy, a thiazide-type diuretic or dihydropyridine CCB

should be initially used.

- ARBs may be better tolerated than ACEi in terms of coughs and angioedema.
- For those with HF or CKD, renin-angiotensin system inhibition should be prescribed.

BP management in the elderly

- Cognitive function:
  - Available data do not show cognitive decline in elderly patients who achieve target BP with antihypertensive therapy (Hispanic Community Health Study/Study of Latinos). Women with uncontrolled BP despite taking antihypertensive medications may have an associated cognitive decline (Women's Health Initiative Memory Study).
  - Intensive versus Standard Ambulatory Blood Pressure Lowering to Lessen Functional Decline in the Elderly—INFINITY trial: Among elderly patients with HTN, intensive lowering of ambulatory SBP reduced the development of subcortical white matter disease and nonfatal CV events but did not improve mobility or cognitive function.
  - SPRINT trial: During a median follow-up of 5.11 years, adjudicated probable dementia occurred in 149 vs 176 participants in the intensive vs standard treatment group respectively (hazard ratio: 0.83; 95% CI, 0.67-1.04). Intensive BP control significantly reduced the risk of mild cognitive impairment (HR, 0.81; 95% CI, 0.69-0.95). SPRINT MIND Investigators for the SPRINT Research Group, JAMA 2018.
- Caution with frail, institutionalized elderly: BP lowering to <130/80 mm Hg with the use of two or more antihypertensive agents in *older nursing home residents* has been shown to be associated with increased mortality (Treatment with Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents Study).

Sodium glucose transporter-2 (SGLT-2) inhibitor effect on BP

- Expressed in S1 and S2 segments of proximal renal tubule where 90% of glucose reabsorption occurs
- Inhibition of SGLT-2 leads to glucosuria, hence glucose control in patients with diabetes and weight loss due to glucose-derived calories.
- Inhibition of SGLT-2 induces mild BP reduction, presumably via an osmotic diuretic effect.

Treatment of resistant HTN

- Ensure compliance with medications and healthy lifestyle modification.
- If on HCTZ, consider switching to thiazide-like diuretic (CTDN or INDAP). Consider switching to loop diuretic if there is poor kidney function and/or evidence of volume overload.
- If already on thiazide-like diuretic, consider adding an MRA.
- Add second-line agents as needed.

HYPERTENSIVE EMERGENCIES

Definition: severe HTN, typically but not always with BP ≥180/120 mm Hg, accompanied by acute and ongoing end-organ damage

Evaluation

Underlying causes: acute head injury or trauma, drug ingestion (prescribed, over the counter, or recreational), recent withdrawal of short-acting antihypertensive agents with known rebound phenomenon (eg, clonidine, β-blockers), pregnancy

Signs and symptoms associated with end-organ injury: nausea/vomiting (increased ICP), dyspnea, chest pain, acute severe back pain

(dissecting aneurysm)

Physical exam: focus on CV and neurologic exams, fundoscopy

Laboratory testing:

- Routine: ECG, urinalysis, basic chemistry, troponin I
- Imaging studies as indicated by signs/symptoms including chest/abdominal CT, brain CT or MRI, (transesophageal) echocardiogram

Clinical Manifestations

- Eye: grades III-IV retinopathy, flame hemorrhages, cotton wool spots, papilledema
- Cerebrovascular: hypertensive encephalopathy, stroke, intracerebral or subarachnoid hemorrhage (cerebral infarction is the most common presentation in ~40%)
- Cardiac: acute aortic dissection, left ventricular failure, or myocardial infarction
- Pulmonary: pulmonary edema (~25%)
- Renal: microangiopathic hemolytic anemia, AKI
- Eclampsia (~2%)

Management of Hypertensive Emergency

Gradual BP reduction is *generally* recommended:

- MAP reduction by ~10% to 20% in the first hour, then by an additional 5% to 15% over the next 23 hours, for a total 24-hour BP reduction <25%

Exceptions to gradual BP reduction over the first day:

Acute phase of ischemic stroke:

- BP NOT lowered unless ≥185/110 mm Hg in candidates for reperfusion therapy

- BP NOT lowered unless ≥220/120 mm Hg for non-reperfusion therapy candidates

Acute aortic dissection: SBP should be lowered to target of 100 to 120 mm Hg *within 20 minutes* and heart rate reduced to <60 beats per minute to reduce aortic shearing.

Acute intracranial hemorrhage:

- For SBP between 150 and 220 mm Hg, acutely lowering SBP to 140 mm Hg is suggested.
- For SBP >220 mm Hg, aggressive SBP lowering to 140 to 160 mm Hg is reasonable.
- For all hypertensive emergencies, keep patient euvolemic to reduce further RAAS activation.

Antihypertensive Medications Used in Hypertensive Emergencies

Nitrates: nitroglycerin, nitroprusside

Nitric oxide induces arteriolar and venous vasodilation by activation of calcium-sensitive potassium channels (via cyclic guanosine monophosphate [cGMP]) in cell membranes.

Nitroglycerin

- Low antihypertensive effect
- Consider use in patients with symptomatic coronary disease or following coronary bypass.
- Limitations: methemoglobinemia with prolonged use >24 hours

Sodium nitroprusside

- Onset of action: <1 minute; activity loss within 10 minutes of discontinuation
- Limitations: cyanide/thiocyanate toxicity: altered mental status, lactic acidosis that may occur within 4 hours
- Risks for adverse effects: high dose, prolonged use >24 hours, poor kidney function
- For high doses (ie, 10 µg/kg/min)

- Do NOT use for more than 10 minutes.
- Add sodium thiosulfate as sulfur donor to detoxify cyanide into thiocyanate.
- Caution:
  - Sodium nitroprusside may lead to reduced coronary, renal, and cerebral perfusion.
  - Sodium nitroprusside and nitroglycerin can potentially increase ICP and reduce cerebral perfusion.

Calcium channel blockers

Clevidipine: ultra-short-acting dihydropyridine CCB (half-life 1 minute)

- Direct arterial vasodilator without altering venous capacitance
- Does not cause tachycardia
- Metabolized in blood and intravascular tissues by esterases; safe for patients with both kidney and liver failure.
- Contraindicated in patients with aortic stenosis (potential severe hypotension), dyslipidemia (mixed in lipid-laden emulsion), and known allergies to soy or eggs

Nicardipine: longer onset of action and longer elimination half-life (3-6 hours)

Selective dopamine-1 agonist: fenoldopam

- Antihypertensive that can maintain or increase renal perfusion
- Avoid in patients with glaucoma and sulfite sensitivity.
- Consider in patients with acute renal hypertensive emergencies.

β-Blockers

Labetalol

- Combined β- and α-adrenergic blocker, good for patients with acute coronary syndrome. Nonetheless, prior administration of α-blockers (eg, phentolamine) should be done prior to using

labetalol in patients with increased adrenergic states (eg, pheochromocytoma, methamphetamine overdose, tyramine ingestion in patients on monoamine oxidase inhibitor).
- Avoid in asthma, chronic obstructive pulmonary disease (COPD), acute HF, or 2° or 3° heart blocks and bradycardia.

Esmolol: cardioselective β-blocker with short half-life and duration of action (9 and 30 minutes, respectively)

Others

Hydralazine

- IV form (arteriolar vasodilator, with possible reflex sympathetic stimulation, ie, tachycardia)
- Avoid in patients with coronary artery disease or aortic dissection.

Enalaprilat (IV form of enalapril, ACEi): may cause excessive hypotension in hypovolemic patients

HTN in Special Situations

Scleroderma renal crisis (SRC)

SRC occurs in 2% to 4% with limited disease (skin involvement *distal to* elbows and knees only) and 5% to 10% of diffuse scleroderma (skin involvement *proximal and distal to* elbows and knees).

Clinical manifestations

- Typically presents early, that is, at diagnosis of scleroderma or 3 to 5 years after disease onset
- Predominant presentation
  - Acute onset of moderate to severe hypertensive urgency/emergency and oliguric AKI
  - Accompanying features: hyperrenin, thrombotic microangiopathy (TMA; 40%-50% of cases), anemia, congestive HF, and/or hypertensive encephalopathy and retinopathy

- 10% of SRC occurs without HTN. This may reflect low baseline BP, underlying cardiac dysfunction, or other reasons to be hypotensive at baseline. "Normotension" at SRC presentation could already be hypertensive for some of these patients.

Risks

- Older age, African American ethnicity, systemic HTN
- Positive anti-RNA polymerase III antibodies
- Early diffuse scleroderma, rapidly progressive skin disease, arthralgia, synovitis, tendon friction rubs, pericardial effusion, pulmonary vasculopathy/HTN, CKD + HTN + proteinuria
- Glucocorticosteroid exposure (eg, >3 months, prednisone >7.5-15 mg qd)

Diagnosis

- Hypertensive SRC
  - SPB >140 mm Hg or DBP >90 mm Hg, or a rise in SBP >30 mm Hg or DBP >20 mm Hg from baseline, AND
  - One of the following features: increase in SCr >50% from baseline or >120% of upper normal limit; proteinuria >2+ by dipstick; hematuria >2+ by dipstick or >10 red blood cells per high-power field (RBC/HPF); thrombocytopenia <100,000 platelets/μL; hemolysis; or hypertensive encephalopathy
- Normotensive SRC
  - Increase in SCr >50% above baseline or SCr >120% of upper normal limit AND
  - One of the following features: proteinuria 2+; hematuria >2+ by dipstick or >10 RBC/HPF; thrombocytopenia <100,000 platelets/μL; hemolysis; renal biopsy with microangiopathy consistent with SRC; or hypertensive encephalopathy

Management of SRC

- ACEis are first-line therapy. ARBs are not adequate as first line to control BP. Other agents may be added to achieve BP goal. β-Blockers are preferably avoided given the theoretical risk of

reduced cardiac output during the high peripheral vascular resistance state.

- Goal: Reduce SBP/DBP by 20/10 mm Hg per 24 hours as needed. Risk reduction: Avoid prolonged (eg, >3 months) high-dose (eg, prednisone >7.5-15 mg qd) glucocorticoid.
- Other considerations requiring more data: eculizumab if concurrent TMA (presumed complement-mediated), endothelin receptor antagonists (eg, bosentan, zibotentan)

Prophylaxis therapy

- None proven effective
- Although ACEis are first-line therapy for SRC, prophylactic ACEi may lead to worse outcome including 2 times increased risk of death and higher likelihood or dialysis dependency. The reason for this discrepancy remains undefined.
- ARBs are not effective. There have been reports of patients developing SRC while receiving ARB.

Renal transplantation

- Effective and improves survival
- Patients should be ≥2 years on dialysis before consideration for transplant due to high recovery rates.
- Recurrence of SRC is <5% and more common in those with early native kidney loss due to SRC.
- Onset of SRC with microangiopathic features in patients receiving CSA has been reported. Whether this is CSA-associated TMA independent of SRC is not known.

Posterior reversible encephalopathy syndrome (PRES)

- Hypertensive syndrome associated with cerebral edema and symptoms of headaches, vomiting, confusion, seizures, cortical blindness
- Acute rise in BP results in dilation of cerebral arteries and arterioles and increase in blood-brain barrier permeability leading to brain edema.

Underlying causes: Vasculitis (lupus), pregnancy (eclampsia), kidney failure, severe HTN. PRES may occur in patients without elevated BP, as seen in some patients receiving immunosuppressive therapy or those with sepsis and multiorgan failure.
Diagnosis: MRI revealing cortico-subcortical areas of hyperintensity involving the occipital and parietal lobes on T2-weighted images
Management:

- BP control and treatment of underlying diseases or withdrawal of offending agents
- Condition may be reversible, but blindness may persist.

Head trauma

Treat if cerebral perfusion pressure (MAP minus ICP) is >120 mm Hg and ICP is >20 mm Hg.

Hypertensive encephalopathy

- Diagnosis of exclusion when mental status improves following BP control
- BP may be lowered by 10% to 20% during the first hour, with a total of 25% lowering within the first 24 hours.
- Consider clevidipine, nicardipine, fenoldopam, nitroprusside
- Goal: Decrease MAP by 15% to 20%.

Acute ischemic stroke

- Consider labetalol or nicardipine.
- Goal: See earlier.

Acute hemorrhagic stroke

- Consider labetalol, nicardipine, or shorter-acting drugs.
- See BP management goal indicated earlier.

Subarachnoid hemorrhage

- Consider labetalol, nicardipine, or esmolol.
- Goal: SBP <160 mm Hg or MAP <130 mm Hg.

Acute HF

- Consider IV sodium nitroprusside, nitroglycerin, or enalaprilat to reduce afterload.
- Avoid hydralazine (can increase cardiac work) or β-blockers, (can decrease cardiac contractility).
- IV furosemide as needed for hypervolemia

Acute coronary syndrome

Consider IV nitroglycerin, clevidipine, nicardipine, or esmolol/metoprolol to reduce myocardial oxygen consumption/ischemia.

Acute hypertensive nephrosclerosis, renal emergencies

- Renal ischemia activates the RAAS, thereby exacerbating the underlying HTN.
- Consider labetalol, nicardipine, or fenoldopam. Fenoldopam is associated with a temporary improvement in renal function and may be useful in renal hypertensive emergencies.
- BP lowering may lead to worsening kidney function, particularly with the use of potent CCB due to the potential vasodilating effect on afferent arterioles and subsequent transmission of systemic HTN into glomeruli.

Acute aortic dissection

- Administer an IV β-blocker (eg, esmolol, labetalol, metoprolol) to reduce HR to below 60 beats per minute.
- Add a secondary vasodilator (eg, nitroprusside, clevidipine, or nicardipine) as necessary to reduce SBP to 100 to 120 mm Hg within 20 minutes.

Ingestion of sympathomimetic agents

- For example, ingestion of tyramine-containing foods in patients on chronic monoamine oxidase inhibitors, cocaine, amphetamine, etc, or severe autonomic dysfunction (eg, Guillain-Barré, Shy-Drager syndromes), acute spinal cord injury
- Administer IV phentolamine or nitroprusside.
- Goal: symptomatic relief
- The use of β-blockers is traditionally contraindicated due to unopposed α-adrenergic vasoconstriction and worsening of HTN. However, some studies have suggested that mixed α/β-blockers such as labetalol and carvedilol may be effective and safe in the setting of ingestion of sympathomimetic agents. Nonetheless, risks and benefits must be weighed for individual cases and close monitoring is required. The nonselective β-blockers labetalol and carvedilol have predominant β-blocking activity with β- to α-blocking ratio of 7:1 or greater.

Autonomic dysfunction

- Guillain-Barré, multiple system atrophy syndromes, or acute spinal cord injury
- Consider phentolamine, nitroprusside, or labetalol

Acute postoperative HTN

- Manage pain and anxiety, and evaluate acute bleed at surgical site.
- Consider nicardipine, labetalol, or esmolol.
- Goal: Achieve preoperative BP.

PREGNANCY AND HTN

BP in Normal Pregnancy

Physiologic changes in BP during pregnancy

- DBP falls by 7 to 10 mm Hg in early pregnancy, by as much as 20 mm Hg in midpregnancy, and returns to baseline by the third trimester.
- SBP only falls slightly due to concurrent 30% to 40% increase in cardiac output and decrease in peripheral resistance.

BP categorization in pregnancy

- Normal BP: <140/90 mm Hg
- Mild to moderate HTN: 140 to 159/90 to 109 mm Hg, confirmed within 4 hours or on two consecutive visits
- Severe HTN: ≥160/110 mm Hg (confirmed within 15 minutes)
- "Normotension" in some pregnant women does not necessarily exclude HTN disorder in pregnancy due to the possibility of low baseline BP prior to pregnancy. SBP >30 mm Hg or DBP >15 mm Hg increase compared with BP prior to pregnancy, but <140/90 mm Hg should be considered and managed as high-risk patients per U.S. National High BP Education Program.

HTN in Pregnancy

Chronic HTN

- Occurs before 20 weeks gestation
- May be primary or secondary HTN
- WCH: SBP ≥140 mm Hg or DBP ≥90 mm Hg office BP, but <135/85 mm Hg using ABPM or HBPM
- Masked HTN: BP <140/90 mm Hg office BP, but ≥135/85 mm Hg outside office BP

Gestational HTN

- Occurs de novo after 20 weeks of gestation in the absence of proteinuria or any finding suggestive of preeclampsia
- Gestational HTN may or may not present as preeclampsia/eclampsia (PE/E).

- Affected women must be instructed to report symptoms consistent with preeclampsia, for example, headaches, visual disturbances, chest pain, dyspnea. Weekly follow-up is advised.

Transient gestational HTN

Occurs de novo after 20 weeks in the clinic setting, which resolves with repeat BP measurements taken serially over several hours in the obstetric same-day observational unit.

Preeclampsia/Eclampsia

Diagnosis

Preeclampsia is gestational HTN with *one or more* of the following:

- Proteinuria ≥300 mg/d or urine protein to creatinine ratio ≥0.3 g/g creatinine
- Evidence of maternal end-organ dysfunction
  - Neurologic complications (eg, severe headaches, altered mental status, blindness, persistent visual scotomata, flashing lights, stroke, clonus, or eclampsia)
  - Pulmonary edema
  - Hematologic complications (eg, platelets $<150 \times 10^3/\mu L$, disseminated intravascular coagulopathy, hemolysis)
  - AKI (in the absence of other known kidney disease)
  - Transaminitis >2 times upper normal limits
- Uteroplacental dysfunction (eg, placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death)

NOTE

The absence of new-onset proteinuria in association with gestational HTN does not exclude preeclampsia. Gestational HTN with evidence for maternal end-organ or uteroplacental dysfunction alone can also define preeclampsia.

Postpartum preeclampsia

- Preeclampsia may be diagnosed postpartum, usually within 48 hours after birth but may be delayed up to 6 weeks.
- Postpartum preeclampsia is not caused by large fragments of retained placenta but is thought to represent a subgroup of patients who had subclinical preeclampsia prior to birth, delayed clearance of antiangiogenic factors, postpartum complement activation, and/or mobilization of extracellular fluid into the intravascular system leading to volume overload, HTN, and cerebral vasoconstriction.
- BP management is similar to preeclampsia.

Eclampsia

Neurologic complication with seizures in a patient with preeclampsia defines eclampsia. This is thought to be due to a form of PRES.

Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP)

- Pathogenesis: thought to be a variant of PE/E
- Clinical manifestations: headaches, chest pain, right upper quadrant abdominal pain, laboratory findings notable for hemolytic anemia, thrombocytopenia (platelet count $<100 \times 10^3$ cells/μL), transaminitis (alanine aminotransferase >70 U/L), and/or AKI. Twenty percent of patients with HELLP do not have either HTN or proteinuria and 20% of women with PE/E with severe features are complicated with HELLP.

Various forms/combinations of HTN seen during pregnancy are summarized in **Table 5.3**.

Table 5.3 Hypertension during pregnancy

	Onset (gestational age)	Characteristic findings and clinical clues
Chronic HTN	Prior to 20 wk	• Left ventricular hypertrophy by electrocardiogram and/or echocardiogram

	Onset (gestational age)	Characteristic findings and clinical clues
		• Presence of secondary cause of HTN • Increased risk for preeclampsia
Transient HTN	After 20 wk	• Transient elevated BP during clinic visit that resolves with repeat BP measurements during the same visit

Preeclampsia	After 20 wk	Preeclampsia is gestational HTN with *one or more* of the following:
		• Proteinuria ≥300 mg/d or urine protein to creatinine ratio ≥0.3 g/g creatinine, and/or
		• Evidence of maternal end-organ dysfunction
		  • Neurologic complications (eg, severe headaches, altered mental status, blindness, persistent visual scotomata, flashing lights, stroke, clonus, or eclampsia)
		  • Pulmonary edema
		  • Hematologic complications (eg, platelets $<150 \times 10^3$/μL, disseminated intravascular coagulopathy, hemolysis)
		  • Acute kidney injury (in the absence of other known kidney disease)
		  • Transaminitis >2 times upper normal limits, and/or
		• Uteroplacental dysfunction (eg, placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death)

Preeclampsia superimposed on chronic HTN	Chronic HTN with worsening of BP after 20 wk	• Presence of any of the preeclampsia features mentioned earlier
Hemolysis, elevated liver enzymes, low platelets (HELLP)	After 20 wk	• Variant of preeclampsia with marked transaminitis (alanine aminotransferase >70 U/L) ± acute kidney injury • 20% of patients with HELLP do not have either HTN or proteinuria.

	Onset (gestational age)	Characteristic findings and clinical clues
		• 20% of women with preeclampsia/eclampsia with severe features are complicated with HELLP.
Postpartum preeclampsia	After delivery	• Usually occurs within 48 h after birth up to 6 wk postpartum • Same presentation as preeclampsia but presents after delivery

Abbreviations: BP, blood pressure; HTN, hypertension.

Pathogenesis of preeclampsia

- In normal pregnancy: Circulating VEGF and transforming growth factor β1 (TGF-β1) bind to their respective receptors VEGFR and TGFR on endothelial cell surface to maintain endothelial health in the kidney and placenta.
- In PE/E:
  - There is excessive placental secretion of soluble fms-like tyrosine kinase 1 (sFLt1) and soluble truncated endoglin (sEng), that bind to circulating VEGF and TGF-β1, respectively. The lowering of free VEGF and TGF-β1 in circulation leads to suboptimal maintenance of endothelial health.
  - This results in endothelial cell dysfunction, decreased prostacyclin and nitric oxide production, and release of procoagulant protein.
  - In addition, proangiogenic factors such as placental growth factor (PlGF) and adiponectin are decreased while antiangiogenic factors such as endostatin are increased.
- Bottomline:
  - High sFLt1 and low PlGF levels increase risk for preeclampsia.
  - The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends the use of angiogenic markers sFLt1/PlGF ratio ≤95th percentile and/or PlGF ≥5th percentile for gestational age to exclude preeclampsia. The absence of

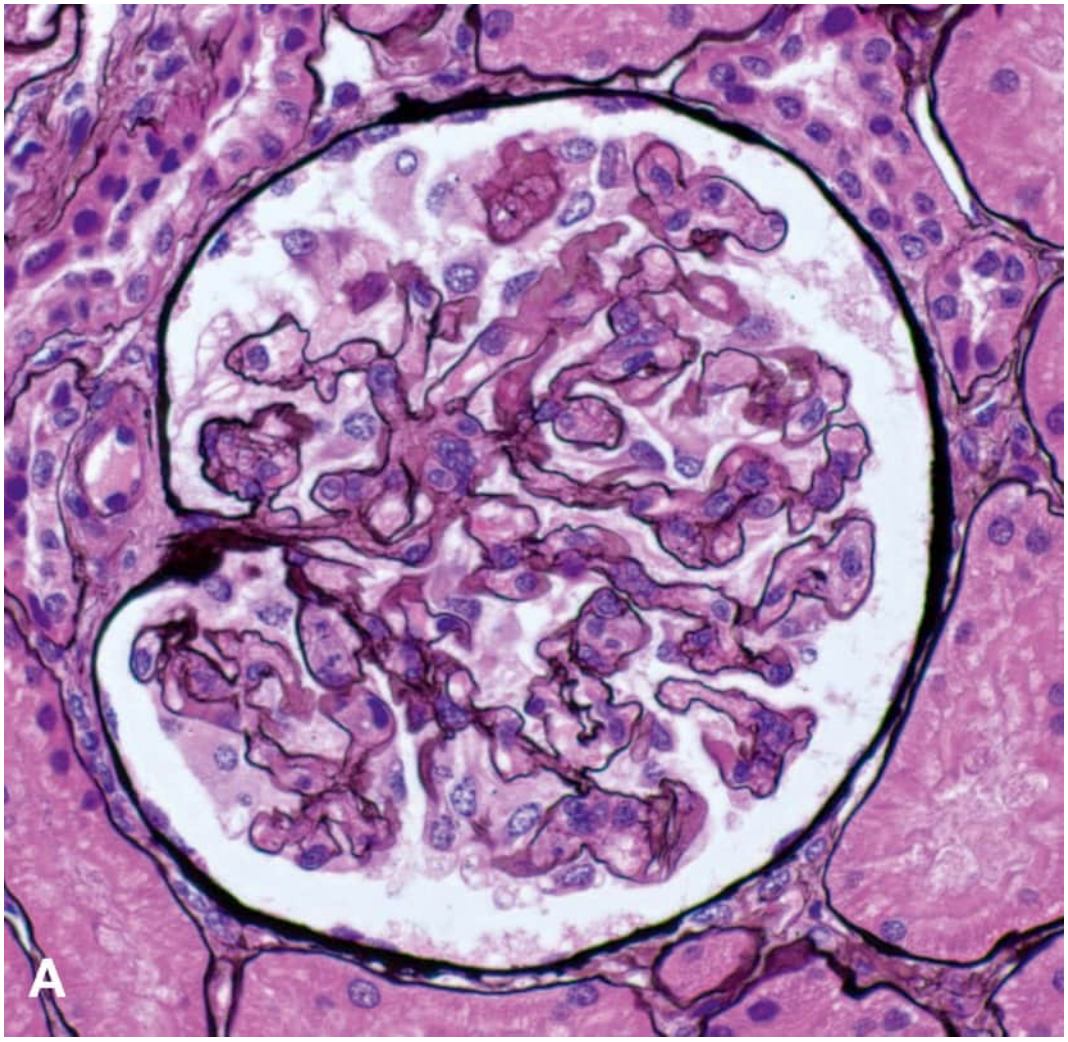
angiogenic imbalance at <37 weeks supports the diagnosis of gestational HTN (without preeclampsia) rather than preeclampsia.

Risks for preeclampsia

- High risks: prior preeclampsia, chronic stage 2 HTN, pregestational DM, CKD, systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, multifetal pregnancy, assisted reproductive therapy for current pregnancy
- Moderate risks: prepregnancy BMI >30 kg/m^2, prior placental abruption, prior stillbirth, prior fetal growth restriction, maternal age >35 years, family history of PE/E, race (black), nulliparity, history of adverse pregnancy outcome, low socioeconomic status
- Online Fetal Medicine Foundation preeclampsia risk calculator

Histopathology

Histopathology (**Figure 5.4**) of kidney injury associated with PE/E: Glomerular tufts are described as "bloodless" with narrowed capillary lumens due to endothelial cell swelling, referred to as "endotheliosis," and intracapillary foam cells may be seen. By electron microscopy, glomerular capillary endothelial cells are swollen with loss of fenestrae. In contrast, capillary loops are wide open and fenestrae are preserved in normal glomeruli. In PE/E, arteries and arterioles do not show features of microangiopathy.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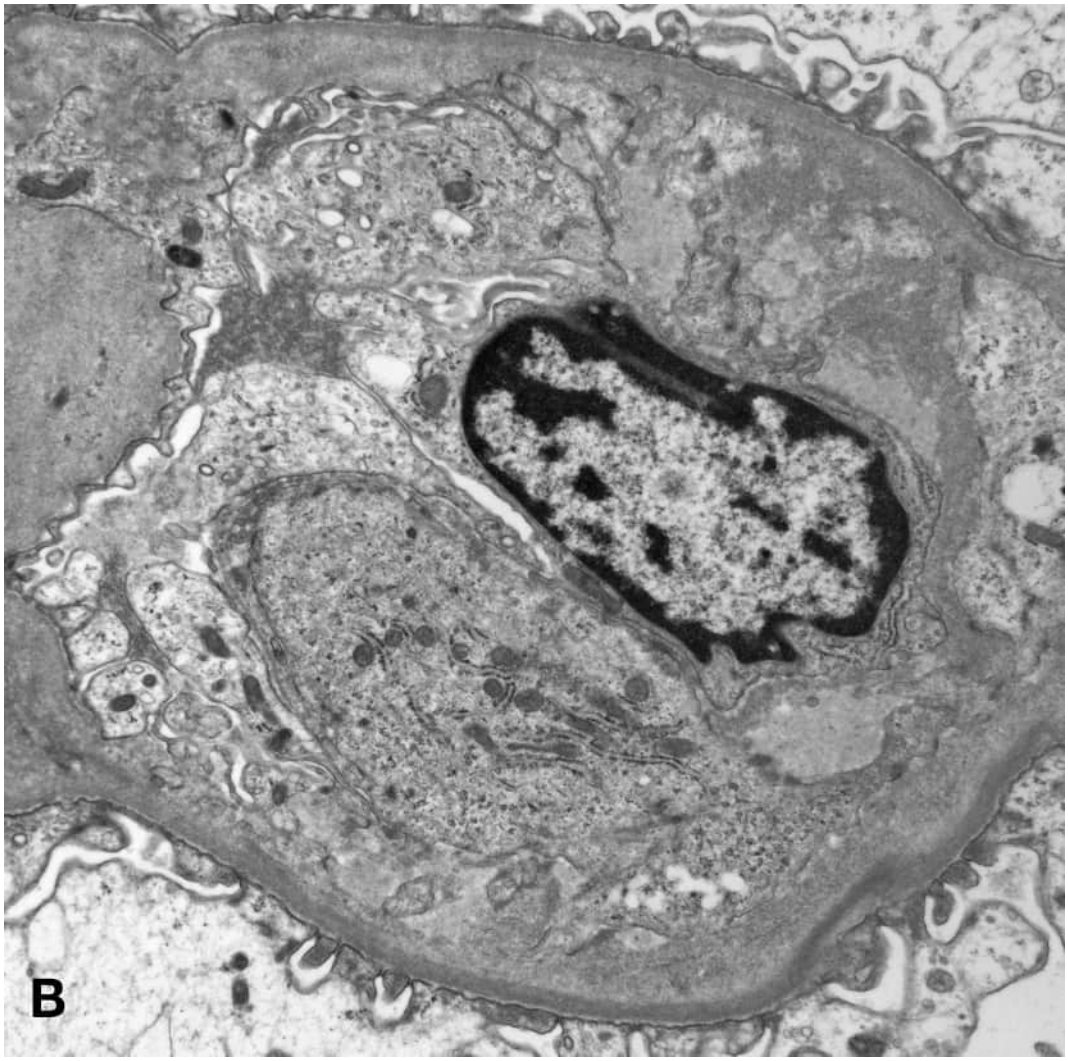
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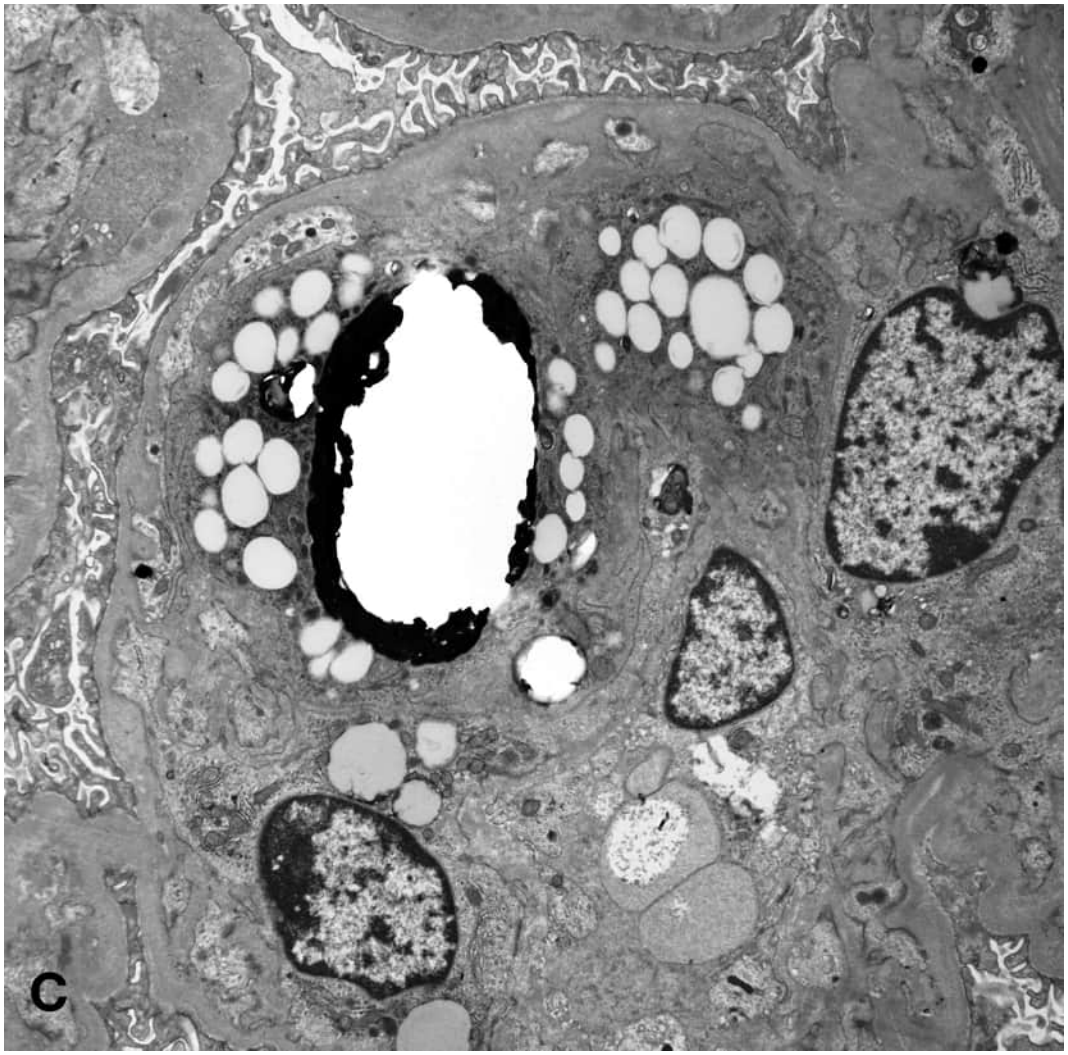

FIGURE 5.4 **Histopathology of preeclampsia/eclampsia.** A. Glomerular capillaries are filled with swollen endothelial cells. There are minor ischemic capillary wall wrinkling and segmental mild podocyte hypertrophy; the adjacent arteriole is normal (Jones methenamine silver ×400). B. Glomerular capillary with swollen endothelial cytoplasm resulting in luminal occlusion. Podocyte foot processes are preserved, but may be effaced (×14,000). C. The capillary lumen has swollen endothelial cell cytoplasm and a foam cell (lipid-filled monocyte) while the podocytes have preserved foot processes (×14,000).

Clinical significance of hypertensive disorders of pregnancy

- Immediate maternal outcomes:
  - Increased mortality, adjusted odds ratio 1.7 to 2.7
  - Increased risks for postpartum hemorrhage and CV events (eg, myocardial infarction, stroke, and peripartum cardiomyopathy, spontaneous coronary artery dissection)

- Immediate fetal/neonatal outcomes: small for gestational age, stillbirth, preterm delivery, placental abruption
- Long-term maternal outcomes: increased risk of HTN, T2DM, hyperlipidemia, CVD, HF, atrial fibrillation, ischemic/hypertensive heart disease, stroke, CKD, venous thromboembolism
- Long-term offspring outcomes: increased risk of CVD (cardiomyopathy, HTN, pulmonary heart disease, arrhythmias, HF), stroke, HTN, increased BMI

Preventive measures

- For women with high risk for PE/E, initiate low-dose aspirin 100 to 150 mg after 12 weeks of pregnancy, preferably prior to 16 weeks, and continue until delivery. Alternatively, some experts suggest discontinuation of aspirin by 36 weeks gestation or 5 to 10 days prior to delivery to reduce bleeding complications.
- Other recommended preventive measures against PE/E include prepregnancy weight loss for obese individuals, moderate-intensity exercise ≥140 min/wk, daily calcium intake 1,000 mg/d (supplement with elemental calcium to achieve goal).
- Not recommended: high-dose folic acid, vitamin C, and vitamin E
- Insufficient data: metformin, statin

Management of HTN in Pregnancy

Antihypertensive agents used for urgent BP control

- Labetalol (IV then switch to oral): Avoid in asthma or HF. Inform neonatologist regarding possible neonatal bradycardia and risk of hypoglycemia.
- Hydralazine (IV or intramuscular): may increase risk of maternal hypotension
- Nicardipine (IV)
- Nifedipine (oral): Associated with reflex tachycardia; extended-release formulations are preferable to minimize risk of acute BP reduction.

Other treatment options for severe HTN

- Nitroglycerin
- Diazoxide (1.5 mg IV) may be comparable to hydralazine (5 mg IV). Note, however, a Cochrane systematic review published in 2013 suggested that diazoxide should probably be avoided given higher risk of hypotension and cesarean section compared with labetalol.

Treatment of nonsevere HTN, (BP <160/110 mm Hg)

Goal BP is below 140/90 mm Hg

Treatment to achieve goal BP has been shown to reduce:

- Risk of severe HTN, transaminitis, thrombocytopenia
- Risk of superimposed preeclampsia with severe features
- Risk for medically indicated preterm delivery <35 weeks gestation
- Placental abruption, fetal/newborn death

Agents to consider:

- Labetalol: 100 to 400 mg orally bid to tid (maximum 1,200 mg/d); monitor for neonatal hypoglycemia and bradycardia.
- Methyldopa: 250 to 500 mg bid to qid, maximum 2 g/d
- Nifedipine, extended release 30 to 60 mg orally daily to bid. Avoid immediate-release formulations due to concerns for potential rapid drop in BP and associated reduction in uteroplacental perfusion.

Inhibitors of RAAS (ACEi, ARB, MRA)

- RAAS inhibitors are contraindicated during pregnancy, particularly after the second half of pregnancy due to fetotoxicity, fetal nephrotoxicity, and stillbirth.
- Theoretically, RAAS inhibitors may be continued up to time of diagnosis of early pregnancy. However, it is prudent to discontinue RAAS inhibitors prepregnancy.

Severe HTN, (BP >160/110 mm Hg)

Rationale for treatment

- Treatment of severe HTN reduces maternal risk of stroke, HF, and other serious cardio- and cerebrovascular complications.
- Note: Benefits of treating mild to moderate HTN developed over the short duration of pregnancy are not clear but may be associated with reduced placental perfusion and increased risk for fetal harm.

When to treat

- Treat when SBP ≥160 mm Hg or DBP ≥110 mm Hg after confirmation by a repeat measurement within 15 minutes.
- Commonly used drugs include parenteral labetalol, parenteral hydralazine, and oral nifedipine.
- Diuretics should be reserved for salt-sensitive HTN only and used at lower doses. It has been suggested that women with preeclampsia have lower plasma volume and the use of diuretics could worsen volume status, thereby causing compensatory vasoconstriction that could worsen the ongoing severe HTN.
- For resistant HTN, consider nicardipine, esmolol, nitroglycerin, nitroprusside.

Treatment goal

- Control BP to achieve SBP 130 to 150 mm Hg and DBP 80 to 100 mm Hg.
- Rate of MAP reduction should be no more than 25% over 2 hours (UpToDate.com, treatment of hypertension in pregnant and postpartum, accessed October 25, 2023 https://www.uptodate.com/contents/treatment-of-hypertension-in-pregnant-and-postpartum-patients/print).
- Avoid aggressive BP lowering, for example, <120/80 mm Hg, to avoid uteroplacental hypoperfusion.

Other supportive therapy: magnesium sulfate

- May lead to a transient decrease in BP at 30 minutes following 2 to 5 g IV dose

- Monitor magnesium toxicity: severe bradycardia, hypotension, hyporeflexia

> **NOTE**
>
> Magnesium has a synergistic hypotensive effect with CCB (eg, nifedipine). This effect may be reversed with IV calcium (ie, 10-20 mL of 10% calcium chloride over 10 minutes, repeat up to 4 times q20min as needed).

Delivery: Expectant management (ie, delivery) may be considered in milder forms of preeclampsia with goal of prolonging pregnancy to full term at 37 weeks.

For eclampsia

- Magnesium sulfate as suggested for preeclampsia
- Treat HTN with agents that do not cause cerebral vasodilation. Labetalol is acceptable. Nicardipine has favorable cerebral hemodynamic effects. Both hydralazine and nifedipine vasodilate cerebral vasculature. However, this should not be the sole criteria for antihypertensive medication selection.
- Captopril may be used for severe postpartum HTN if breastfeeding is not considered.

For postpartum HTN

Treat as per nonpregnant population but adjust medications based on breastfeeding safety.

> **NOTE**
>
> The use of VEGF inhibitors (eg, bevacizumab and sunitinib) may give rise to a clinical entity similar to that seen in preeclampsia with severe HTN.

Orthostatic Hypotension

- SBP falls of >20 mm Hg within 2 to 5 minutes of quiet standing from supine or >15 mm Hg from sitting position

- Management goal: Maintain functioning patient, not achieving specific BP goal.
  - Nondrug: Increase fluid and salt intake, avoid getting up quickly or prolonged motionless standing, use compressive waist-high stockings, raise head of bed by 6 to 9 in, maintain active lifestyle.
  - Drug options: midodrine, fludrocortisone, and pseudoephedrine
    - If supine HTN: Consider midodrine on as-needed basis (prn).
    - If no supine HTN: Consider fludrocortisone or midodrine prn. Combination therapy if necessary
    - Droxidopa, a precursor of NE, is an oral vasopressor agent that has been approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of neurogenic orthostatic hypotension. Action onset and duration of action are 1 and 6 hours, respectively. Nighttime HTN may be significant in some patients.

Orthostatic HTN

- SBP rise of >20 mm Hg with standing
- Prevalence estimated at 5% among older hypertensive patients from SPRINT data
- Management:
  - No specific recommendations given due to lack of data
  - Consider nighttime α-blocker doxazosin or central acting α-agonist clonidine.
  - Use of daytime venous stock compression may be considered to prevent venous pooling and fluctuation in central venous return.

Both orthostatic hypotension and HTN are associated with increased risks for CV events.

CHAPTER 6

Tubular, Interstitial, and Cystic Disorders

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RENAL TUBULAR DISORDERS AND FANCONI SYNDROME

Fanconi Syndrome

Fanconi syndrome refers to proximal tubular dysfunction causing renal wasting of low-molecular weight (LMW) proteins, glucose, bicarbonate, phosphate, uric acid, carnitine, and others.

Clinical manifestations of Fanconi syndrome

Notable urinary findings

- Glucosuria in the absence of hyperglycemia
- Low-level proteinuria due to inability of proximal tubules to reabsorb LMW proteins that are normally filtered
  - LMW proteinuria is known as "tubular proteinuria," which typically totals less than 1.0 to 2.0 g/d and comprises less than 25% albumin.
  - Examples of LMW proteins: amino acids, β2-microglobulin, cystatin C, retinol-binding protein, α1-macroglobulin

Electrolyte abnormalities

- Hypophosphatemia: Phosphaturia is typically only seen in early disease. Once new steady state has been achieved, the degree of phosphaturia matches intake.
- Bicarbonaturia and associated sodium wasting (leading to polyuria and volume depletion)
- Hypokalemia: This is likely due to the high potassium filtered load associated with acidemia and increased distal sodium delivery to epithelial sodium channel (ENaC) resulting in subsequent potassium loss.

Metabolic effects

- Metabolic acidosis due to reduced bicarbonate reabsorption
- Hypouricemia due to hyperuricosuria
- Carnitine deficiency (Carnitine is required for the transport of fatty acids from cytosol into mitochondria during the breakdown of lipids for the generation of metabolic energy. Carnitine deficiency has been implicated in poor fatty acid metabolism, reduced antioxidant activities, poor glucose control, and osteoporosis.)

- Rickets, osteomalacia, and growth failure due to reduced proximal tubular $1,25(OH)_2D_3$ production due to reduced 1-α hydroxylase activity, chronic metabolic acidosis, and electrolyte disturbances related to calcium, phosphate, and magnesium

Conditions associated with Fanconi syndrome

Inherited conditions

- Cystinosis: Most common inherited condition associated with Fanconi syndrome; associated with defective tubular reabsorption of **C**ystine, **O**rnithine, **L**ysine, and **A**sparagine, known as *COLA*. Unlike the other amino acids, cystine has low solubility and easily crystallizes in renal tubules to form cystine stones.
- Others: galactosemia, hereditary fructose intolerance, tyrosinemia type 1, glycogenosis, Wilson disease (inherited disorder involving copper metabolism), oculocerebrorenal syndrome (aka Lowe syndrome, an X-linked mutation involving the enzyme phosphatidylinositol [4,5]-bisphosphate 5-phosphatase in the trans-Golgi network, associated with severe bilateral cataracts and hypotonia at birth), mitochondrial cytopathies

Acquired

- Heavy metals: lead, cadmium, mercury, platinum
- Drugs: cisplatin, ifosfamide, imatinib, gentamicin, rifampin, expired tetracycline, tenofovir, adefovir, azathioprine (AZA), valproic acid, suramin, streptozocin, ranitidine, nucleoside reverse transcriptase inhibitors including abacavir, didanosine, and lamivudine and both formulations of tenofovir (tenofovir disoproxil fumarate, tenofovir alafenamide)
- Other exogenous agents: glue sniffing, diachrome, some herbal medicines
- Dysproteinemias: multiple myeloma/light chain nephropathy (most common condition associated with Fanconi syndrome in adults), amyloidosis, Sjögren
- Others: acute tubular necrosis, nephrotic syndrome, renal transplantation

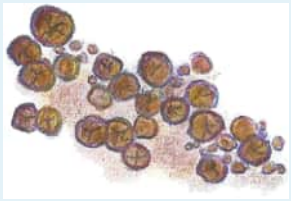
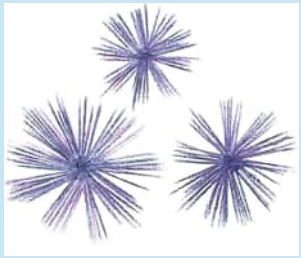
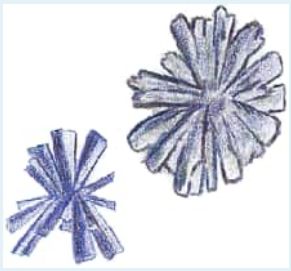
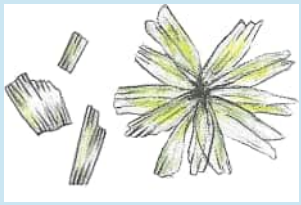
Crystalluria

Crystal nephropathy: Precipitation/crystallization of inciting agents within renal tubules leads to microtubular obstruction and associated tubulointerstitial nephritis.

Risk factors for drug crystallization: supersaturation of drug level in urine, volume depletion (low urine flow), urine pH, reduced levels of inhibitors for crystallization

Common inciting agents (Table 6.1)

Table 6.1 Drug-induced crystalluria

Crystals	Comments	Crystals	Comments
	Sulfadiazine • Resemble "shock of wheat," "bow tie" • Risks: dose >4-6 g/d, urine pH <5.5, volume depletion • Management: alkalinize urine >7.15		**Methotrexate** • Risks: low urine pH, low urine flow • May also be nephrotoxic • Management: alkalinize urine to pH >6.0, fluid support
	**Ciprofloxacin** • Needles, stars, fan-shaped crystals • Risks: older age, urine pH >7.0 • Management: Avoid use in older patients and concurrent use with alkalinizing agents.		**Triamterene** • Risks: low urine pH • Spherical, brown crystals, may resemble Maltese crosses under polarized light • Management: use low dose with fluid support, alkalinize urine
	Acyclovir • Risks: rapid intravenous bolus therapy, volume depletion • Management: use low dose, slow infusion, normal saline support		**Calcium phosphate** • Oral sodium phosphate (bowel preparation) • Risks: volume depletion, use of RAAS inhibitors, diuretics, NSAIDs, high urine pH • Avoid use in CKD and older patients.
	**Indinavir (protease inhibitor)** • Other protease inhibitors also reported to cause crystal nephropathy (**darunavir, atazanavir**). • Management: fluid support		**Calcium oxalate** • Crystals may take octahedral, dumbbell, or picket-fenced shape. • Orlistat (inhibitor of gastric and pancreatic lipase, induces fat malabsorption), vitamin C, star fruit, rhubarb leaves, cranberry juice, nuts, ethylene glycol

Crystals	Comments	Crystals	Comments
	Ampicillin • Risks: high dose, acidic urine • Management: fluid support particularly with high dose		**Hippurate** May be seen with toluene ingestion

Abbreviations: CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system.

Drugs/exposures: sulfadiazine, ciprofloxacin, acyclovir, indinavir, atazanavir, darunavir, methotrexate, triamterene, orlistat, megadose of vitamin C (oxalate), oral sodium phosphate, ampicillin, foscarnet, pseudoephedrine, ethylene glycol (found in antifreeze, metabolizes to oxalate)

Natural sources: star fruit, rhubarb leaves, cranberry juice (oxalate); Ma Huang (ephedrine); Djenkol beans (needle-like crystals)

Clinical associations: gastric or intestinal bypass, pancreatitis (oxalate)

Management: drug withdrawal and fluid support

Figure 6.1 shows tubular injury due to intraluminal crystals.

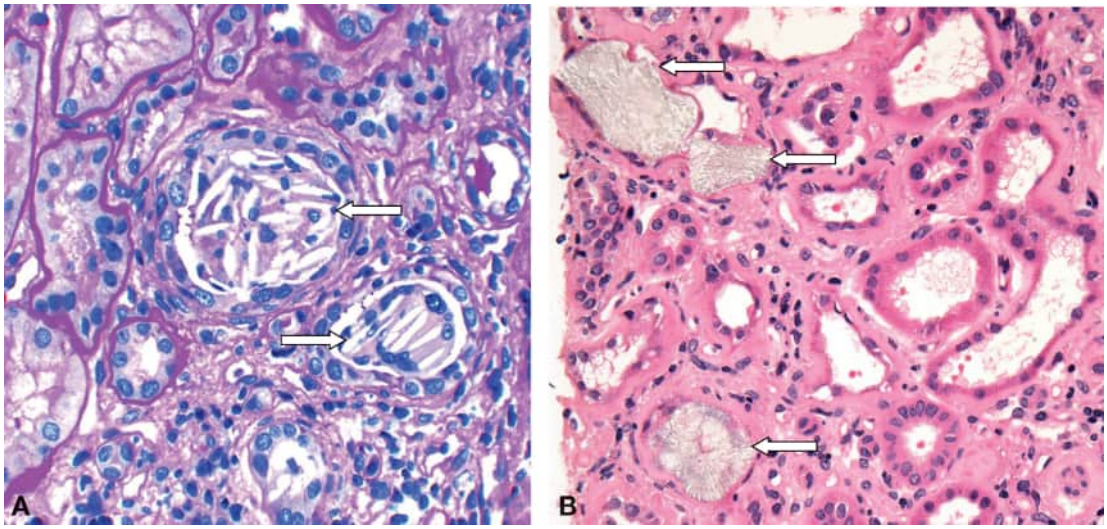


FIGURE 6.1 **Tubular injury due to intraluminal crystals.** A. Indinavir crystals are within the lumina of tubules (arrows) admixed with sloughed epithelium (periodic acid-Schiff ×400). B. There are clear to yellow crystalline aggregates of oxalate within tubular lumina (arrows) with tubular cell flattening, simplification and attenuation, and relative dilatation of tubular lumina (hematoxylin and eosin ×250).

INTERSTITIAL/TUBULOINTERSTITIAL NEPHRITIS

Acute Interstitial Nephritis (AIN)

AIN may be caused by infections, drugs, environmental exposures, autoimmune diseases, inherited conditions, or underlying glomerular disease.

Epidemiology of AIN

Overall prevalence of biopsy-proven AIN is 2% to 5% and ranges between 6.5% and 35% of biopsies performed for acute kidney injury (AKI).

Prevalence of AIN by etiologies

- 70% to 75% are drug induced (eg, antibiotics [in particular, β-lactam, sulfonamides, rifampin, fluoroquinolones], nonsteroidal anti-inflammatory drugs [NSAIDs], proton pump inhibitors [PPI], checkpoint inhibitors [CPIs; eg, inhibitors of cytotoxic T-lymphocyte-associated protein 4 [CTLA-4; ipilimumab], programmed cell death protein-1 [PD-1; nivolumab, pembrolizumab, cemiplimab], and programmed death ligand-1 [PDL-1; atezolizumab, avelumab, durvalumab]], among others).
- 10% are related to infections (more common in children and developing countries).
- 10% to 20% are due to autoimmune diseases, for example, sarcoid, Sjogren, systemic lupus erythematosus (SLE).
- 5% are associated with rare autoimmune diseases (anti-tubular basement membrane [anti-TBM] disease, tubulointerstitial nephritis and uveitis [TINU], and immunoglobulin G4-related disease [IgG4-RD]).
- Less than 5% involve other causes including hereditary/toxic/metabolic conditions, for example, hyperoxaluria, heavy metal toxicity, hyperuricemia, hypercalcemia.

Pathogenesis of AIN

Drug-induced AIN is idiosyncratic, host dependent, unrelated to drug dose, and recurs with reexposure. Suggested mechanisms of AIN include:

Hapten: The inciting agent (ie, drug or infection) acts as a hapten. That is, the inciting agent binds to an otherwise nonimmunogenic native kidney protein (eg, albumin or host amino acid) and renders it immunogenic.

Prohapten: The inciting agent is a prohapten which becomes a hapten after it has been digested or metabolized by the host.

Pharmacologic interaction: The inciting agent binds to host human leukocyte antigen (HLA) molecules and is presented to T cells.

Circulating immune complexes formed against the inciting agent deposit into the kidney interstitium and induce an inflammatory immunologic response that can be either cell- (predominant) or antibody mediated (less common).

- Cell mediated: Kidney biopsy typically reveals predominant T-cell infiltrates in interstitium.
- Antibody mediated: Most biopsies do not reveal immune complex deposits. In some cases, immune complex deposits may be seen in TBM.

Infection: Infectious agents cause an innate inflammatory response, and there may be inflammation secondary to parenchymal injury.

Clinical manifestations of AIN

Classic triad of skin rash, leukocyturia, and fevers

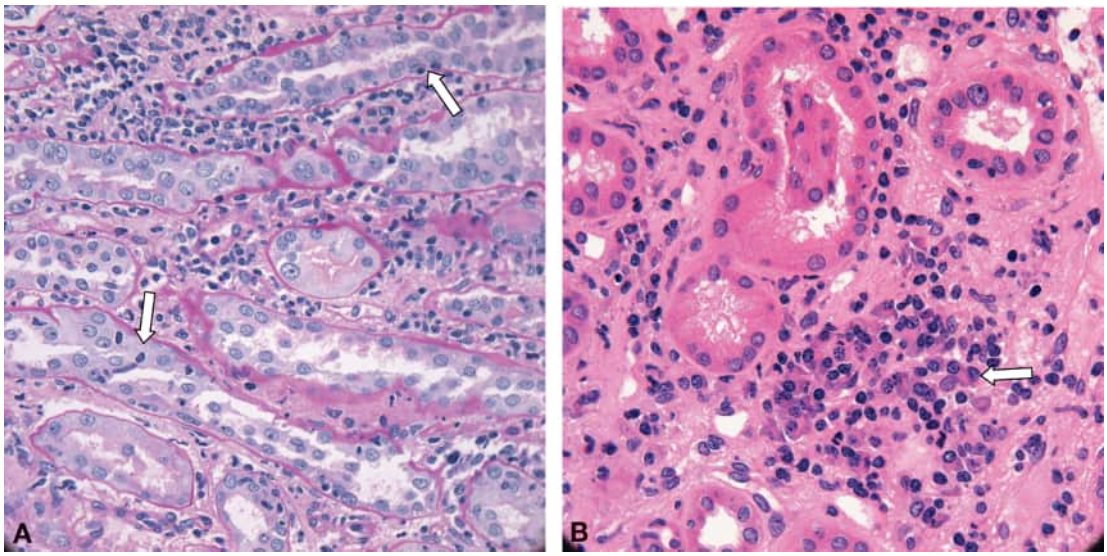
- Not commonly seen; may be seen in less than 10% of cases
- Classic triad may be commonly seen with antibiotic-induced AIN (particularly penicillin derivatives) but not common with NSAIDs-associated AIN.

AKI and sub-AKI

- Onset of kidney injury
  - Typically occurs within 7 to 14 days of exposure to the inciting agent but may occur within 2 to 3 days with reexposure or subacute over months
  - 7 to 14 days of exposure to antibiotics
  - Weeks to months of exposure to NSAIDs and CPIs
  - Months of exposure to PPI
- Of note, de novo kidney injury from a medication previously tolerated may be observed.

Fanconi syndrome and renal tubular acidosis—rare

Histopathology of AIN (Figure 6.2)



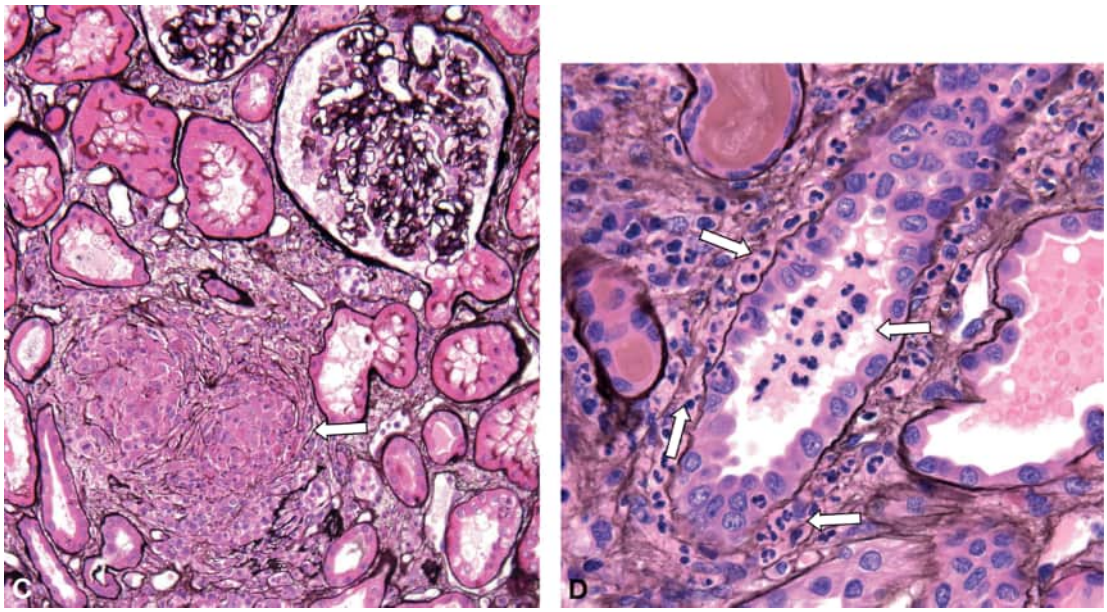


FIGURE 6.2 Acute tubulointerstitial nephritis. A. The interstitium is expanded due to edema and an infiltrate of lymphocytes, which also are in the walls of tubules (arrows) with acute tubular cell injury (periodic acid-Schiff ×250). B. Interstitial edema and inflammation with prominent plasma cells (arrow) admixed with lymphocytes and macrophages (hematoxylin and eosin ×350). C. Granulomatous interstitial nephritis. There is a nonnecrotizing granuloma (arrow) in the interstitium composed of epithelioid histiocytes (periodic acid methenamine silver ×200). D. Neutrophils (arrows) are in the interstitium, and tubular walls and lumen in infection (pyelonephritis) (periodic acid methenamine silver ×425).

Light microscopy (LM)

- Acute interstitial injury is characterized by edema. Interstitial inflammatory infiltrates are present and may be diffuse but often are patchy, predominating in the deep cortex and outer medulla. Inflammatory cells are primarily T cells with monocyte/macrophages and variable plasma cells, some eosinophils, and few neutrophils.
- Tubulitis may be seen in AIN. Tubulitis refers to leukocyte, predominantly lymphocytic, infiltration into the tubular walls between epithelial cells. When frequent, this may be termed tubulointerstitial nephritis.
- Granulomas may be seen in AIN or chronic interstitial nephritis (CIN) associated with autoimmune disease (sarcoidosis, Sjogren syndrome, TINU), infections (eg, tuberculosis, leprosy, histoplasmosis, xanthogranulomatous pyelonephritis), crystals/foreign bodies (eg, urate, oxalosis, recreational drug impurities), medications (eg, sulfas, synthetic penicillins, NSAIDs, thiazides, levofloxacin, checkpoint inhibitors), and surrounding areas of injury (glomerular rupture due to crescents, tubular rupture).
- Neutrophils are present in the interstitium, tubular walls, and lumens in infection-associated AIN (bacterial pyelonephritis).

Immunofluorescent (IF) microscopy and electron microscopy (EM)

- IF and EM are typically negative for immunoglobulins and C3 (most AINs are cell mediated, not antibody mediated).
- In some instances, antibodies may be formed linearly against antigens or drugs bound to the TBM (eg, methicillin, NSAIDs, phenytoin, allopurinol).
- Kidney biopsies from patients with AKI from Hantavirus infection, anti-brush border disease (LDL [low-density lipoprotein] receptor-related protein 2 [LRP2] nephropathy) and IgG4-RD may reveal granular immune deposits along the TBM and also in 20% to 50% of cases in the glomeruli.

Drug-induced AIN

Common drugs associated with AIN: antibiotics (particularly β-lactams, sulfas), NSAIDs including cyclooxygenase-2 (COX-2) inhibitors, PPI, CPI, diuretics, etc

NSAIDs and COX-2 inhibitors may induce kidney injury via various mechanisms:

- Acute tubular necrosis due to acute afferent arteriolar vasoconstriction and resultant reduction in intraglomerular filtration pressure
- Interstitial nephritis which may present as acute, chronic, or granulomatous disease
- Papillary necrosis in patients with underlying ischemic conditions (eg, diabetes mellitus and associated arteriosclerosis, sickle cell disease)
- Up to 75% of NSAID-induced AIN is associated with nephrotic syndrome and glomerular lesions including minimal change disease, membranous nephropathy, less commonly focal segmental glomerulosclerosis (FSGS), and rarely membranoproliferative glomerulonephritis. Risks include older age, chronic use, and use of fenoprofen.

Rifampin

- Likely the *leading cause* of AIN ± ATN among patients receiving therapy for antituberculosis, although pyrazinamide and isoniazid may also induce AIN
- Consider switching to levofloxacin (consult infectious disease specialist).

Allopurinol

- Thought to be due to immunologic reactions between the metabolite oxypurinol with purines, ribonucleoproteins, and nucleic acids. Accumulation of oxypurinol increases with reduced kidney function. Dose reduction in chronic kidney disease (CKD) is recommended.
- Clinical manifestations: AIN ± granulomas, diffuse maculopapular rash, toxic epidermal necrolysis, exfoliative dermatitis, hepatic necrosis, cholangitis

Antihistamines

- Suggested pathogenesis: Histamine stimulates a subset of suppressor T cells via H2 receptors. Blockage of H2 receptors may lead to increased cell-mediated responses.
- Antihistamines associated with AIN include cimetidine, ranitidine, famotidine.
- Cimetidine-induced AIN has also been reported to be associated with positive antineutrophil cytoplasmic antibodies (ANCA; against both MPO [myeloperoxidase] and PR3 [proteinase 3]) serology.

- Famotidine-induced AIN has been suggested to be due to autoantibody formation against carbonic anhydrase II.

5-Aminosalicylates (sulfasalazine, mesalamine, olsalazine): AIN typically occurs within the first year of use.

Oxalate nephropathy presenting as calcium oxalate crystal nephropathy and AIN: ascorbic acid (vitamin C), star fruit, orlistat (induces malabsorptive state that promotes gastrointestinal [GI] oxalate absorption, also occurs with GI bypass or intestinal surgery), rhubarb leaves, excessive nuts, ethylene glycol (antifreeze)

Checkpoint inhibitors

- Checkpoint proteins are T-cell surface proteins that serve to dampen immune responses from T cells upon interaction with antigen-presenting cells. *CPIs* allow T cells to remain "unchecked" in their active state to attack foreign antigens or tumor cells. Two checkpoint proteins that have been targeted in oncology include the CTLA-4 and the PD-1. Inhibitors against these checkpoint proteins allow T cells to remain in their active state to fight tumor cells. The unchecked active T cells, however, can mount a more aggressive and/or sustained response to any AIN-prone drugs or self-antigens associated with autoimmune diseases. That is, a subclinical AIN from a drug such as PPI may be unmasked as overt AIN during CPI therapy for underlying malignancy.
- AIN ± granulomatous features have been reported with CTLA-4 and PD-1 inhibitors:
  - CTLA-4 antagonist ipilimumab: AIN presents within 6 to 12 weeks after initiation of therapy ± associated podocytopathy (eg, minimal change disease, FSGS, membranous nephropathy).
  - PD-1 inhibitors (eg, nivolumab, pembrolizumab): AIN presents within 3 to 12 months ± associated podocytopathy.
- Inflammatory responses involving other organs (eg, thyroiditis, hepatitis, colitis, dermatitis, pancreatitis) may also occur with the use of CPIs.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

- Clinical manifestations: fevers, facial edema, skin lesions (diffuse macular/papular erythematous lesions with lymphocytic infiltrates, exfoliative dermatitis), lymphadenopathy, multiorgan inflammatory response (eg, pneumonitis, hepatitis, AIN)
- Laboratory findings: eosinophilia, lymphocytosis, elevated aminotransferase (ALT [alanine aminotransferase])
- Reported responsible agents: phenytoin, phenobarbital, allopurinol, sulfonamides, dapsone, vancomycin, minocycline, raltegravir, vemurafenib, lenalidomide, β-lactams
- Treatment: drug withdrawal, supportive care, steroids

Other reported drug-induced AIN: liraglutide, varenicline, rosuvastatin, kudzu root (Japanese arrowroot) juice ingestion, B-rapidly accelerated fibrosarcoma oncogene inhibitors vemurafenib and dabrafenib (used for BRAF V600E mutation-positive melanoma, lung, colorectal carcinoma), linezolid, clindamycin

Infection-related AIN

- May involve various bacteria, viruses, parasites, atypical microorganisms, fungi
- Granulomatous AIN may be seen, particularly with fungal, mycobacteria, and parasites.
- AKI during treatment of infections may result from infection-related AIN independent of antibiotic/treatment.

Glomerular disease–associated AIN: Nonselective proteinuria or crescentic injury involving proinflammatory proteins and growth factors may induce a peritubular inflammatory response, complement activation, and progressive interstitial fibrosis.

Immunologic or autoimmune-mediated AIN

Associated with systemic diseases: sarcoid, Sjogren, TINU, IgG4-RD, SLE, ANCA-associated disease, IgM plasma cell interstitial nephritis, primary biliary cirrhosis

Tubulointerstitial nephritis and uveitis

- More commonly seen in adolescents and young women
- Thought to be an autoimmune disease with possible autoantibody formation against modified C-reactive protein, an antigen present in both uvea and renal tubular cells
- Risk factors:
  - HLA-DQA1*01, HLA-DQB1*05, and HLA-DRB1*01
  - Use of antibiotics, NSAIDs, Chinese herb "goreisan"
  - Concurrent *Chlamydia* and Epstein-Barr virus infection
  - Autoimmune diseases involving parathyroid or thyroid, IgG4-related autoimmune disease, and rheumatoid arthritis
- Clinical manifestations: painful red eyes (uveitis), AIN, possibly transaminitis, nonspecific system symptoms, for example, fevers, weight loss, malaise, abdominal/flank pain, arthralgias, myalgias, urinary signs and symptoms including polyuria, nocturia, hematuria, proteinuria, evidence of proximal and distal tubular dysfunction, Fanconi syndrome
- Renal disease may precede ocular disease by years.
- Differential diagnosis: vasculitis, tuberculosis, fungal infections, sarcoidosis, Sjogren
- Treatment: prednisone 1 mg/kg/d × 3 to 6 months with slow taper. Addition of cytotoxic agent may be necessary (eg, mycophenolate, calcineurin inhibitor).

Primary renal AIN with tubulointerstitial immune complex deposits

- Anti-LRP2 nephropathy:
  - Rare anti-brush border antibody condition with autoantibody directed against LRP2 (megalin)
  - Abundant IgG4-positive plasma cells may be seen.
- Idiopathic hypocomplementemic tubulointerstitial nephritis: These are likely manifestations of other diseases (anti-LRP2 nephropathy, lupus nephritis, IgG4-RD).

- Giant cell tubulitis with TBM immune deposits

Anti-TBM nephritis

Primary AIN with linear IgG deposition along TBM, without immune complex deposits

Other causes of AIN: heavy metals, herbal products, idiopathic

Kidney transplant setting

AIN may occur due to acute cell-mediated rejection in the allograft, immunosuppressive therapy, and infections, particularly polyomavirus B-cell lymphoma kinase (BK) nephropathy, cytomegalovirus (CMV) and adenovirus nephritis.

Diagnosis of AIN

Abnormal urine sediment

- Routine urinalysis
  - Presence of leukocytes: 50% to 60% of all cases of AIN
  - Microscopic or gross hematuria: approximately 50%
  - Eosinophils: less than 50%
  - White blood cell casts: less than 5%
  - Granular casts: less than 50% to 70%
  - Low-grade tubular proteinuria: less than 1 to 2 g/d, occurs in approximately 90%
- Eosinophiluria
  - Eosinophiluria is not a sensitive marker for AIN. Eosinophils may not shed into urine and/or lyse prior to visualization.
  - Eosinophiluria is not specific to AIN. It may also be seen with urinary tract infections, prostatitis, bladder malignancy, and glomerulonephritis.
  - The routine use of urine eosinophils to diagnose suspected AIN is not recommended.
- Proteinuria
  - Non-nephrotic range, predominant LMW tubular proteinuria
  - Nephrotic range proteinuria is possible, particularly when there is concurrent podocytopathy, for example, NSAIDs, CPIs.

Blood tests:

- Elevated SCr
- Leukocytosis with eosinophilia (≥500 eosinophils/μL)
- Others: anemia, elevated erythrocyte sedimentation rate, transaminitis; ANCA may be positive without associated glomerular disease.

Gallium scan:

- Gallium binds to lactoferrin on white blood cells, originally thought to be specific to AIN, but later found to be positive in other conditions as well (eg, glomerular diseases, pyelonephritis, atheroembolic disease).
- Poor sensitivity and specificity and NOT recommended for the diagnosis of AIN

Kidney biopsy is the gold standard
For future directions in the diagnosis of AIN not yet available clinically, see**Appendix A6.1.**

Prognosis of AIN

- Recovery depends on duration of drug exposure, duration of AKI, and severity of interstitial fibrosis and tubular atrophy.
- Recovery may take several weeks. 50% recover fully, while the other 50% will have persistently elevated serum creatinine.

Management of AIN

- Supportive, dialysis as needed
- Prompt removal of offending agent
- Glucocorticoids (GC) may be considered.
  - Early initiation of less than 7 days is most important. GC may lead to prompt recovery *if given early* but not necessarily overall outcome.
  - Lower degree of fibrosis is associated with better response to GC. Avoid GC if greater than 75% scarring on biopsy (expert opinion).
  - There is no consensus on optimal GC dose. Consider pulse intravenous (IV) methylprednisolone, 250 to 1,000 mg qd × 3 days, followed by prednisone 1 mg/kg/d (maximum 80 mg qd) × 3 months (ASN Annual Scientific Meeting, 2019, AIN session)—taper per response/discretion of the treating physician.
  - Consider systemic GC if severe systemic involvement (eg, DRESS).

CHRONIC INTERSTITIAL NEPHRITIS

CIN is characterized by interstitial fibrosis (as opposed to edema in acute injury) and tubular atrophy with, and less often without, significant mononuclear inflammatory infiltrate. When there is minimal inflammation, it may be termed chronic interstitial nephropathy.

Clinical Manifestations of CIN

Patients are typically asymptomatic with incidental abnormal laboratory findings:

- Mild proteinuria of less than 1.5 g/d
- Proteinuria predominantly consists of LMW tubular proteins.
- "Bland" urinalysis: no (or rare granular) casts, minimal white and/or red blood cells
- Anemia severity is out of proportion to the degree of kidney injury due to damage of peritubular erythropoietin producing cells in CIN.
- Other signs of tubular injury may be present: sodium wasting, metabolic acidosis, Fanconi syndrome, nephrogenic diabetes insipidus
- Kidney biopsy is the gold standard for diagnosing CIN.

Histopathology of CIN (Figure 6.3):

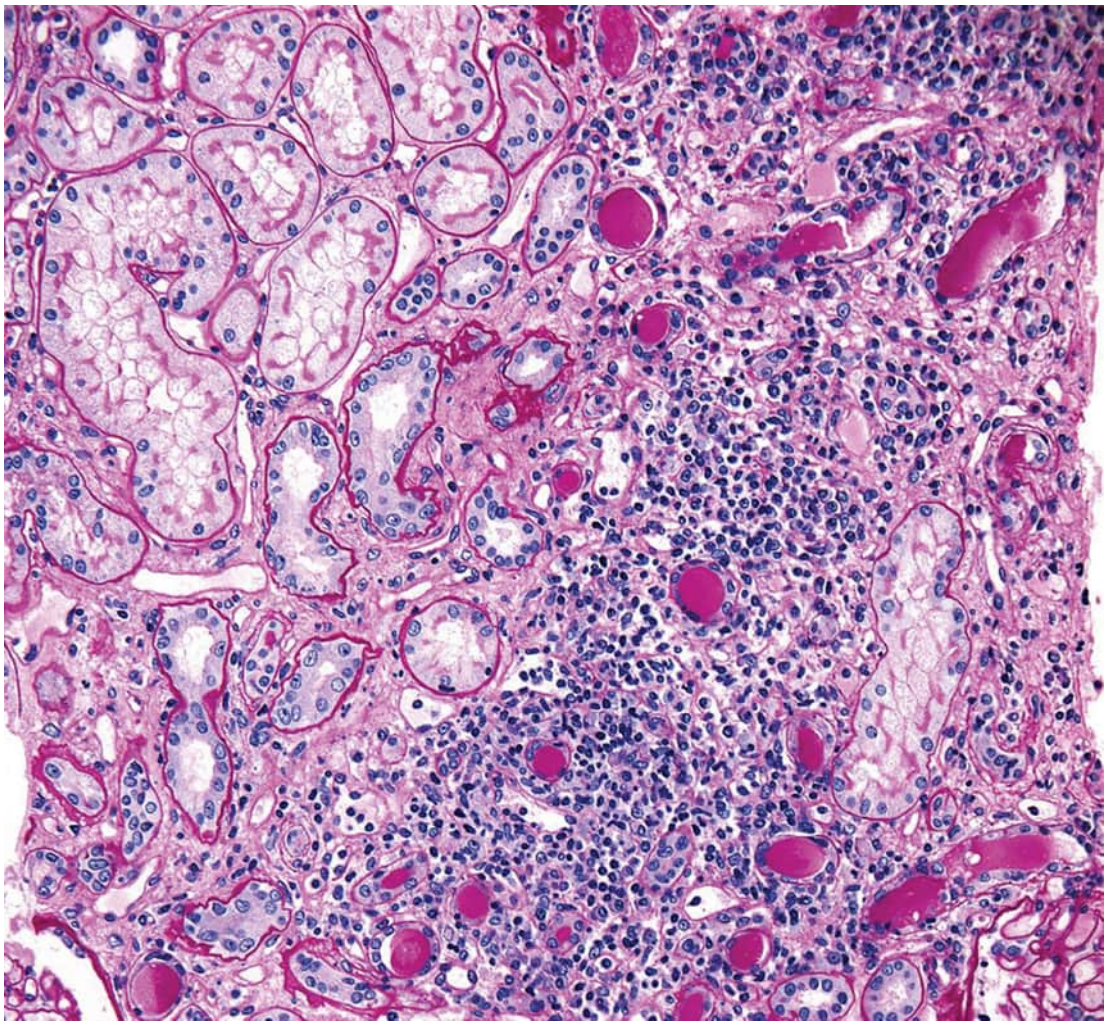


FIGURE 6.3 **Chronic interstitial nephritis.** The interstitium focally shows fibrosis with tubular atrophy and a lymphocytic infiltrate, which is restricted to the area of parenchymal scarring. Note the adjacent preserved tubulointerstitium in the upper left corner, in which there is no inflammation (periodic acid-Schiff ×200).

- Interstitial fibrosis (not edema) with an associated mononuclear inflammatory infiltrate, typically lymphocytes and macrophages with variable plasma cells
- Tubular atrophy

CIN Causes, Diagnosis, and Management

Common causes of CIN include drugs, crystals (eg, calcium phosphate, uric acid, oxalate), infections, autoimmune, obstruction, chronic ischemia, heavy metals

Drug-induced CIN

Analgesic nephropathy

- Traditionally, analgesic nephropathy referred to the chronic use of the drug mixture containing (phenacetin, paracetamol, or acetaminophen) plus (salicylate) plus a potentially addicting agent (caffeine or codeine). Any of the drugs belonging to the first group can be metabolized to acetaminophen and its toxic metabolites which require glutathione for detoxification. Accumulation of the toxic metabolites may form covalent bonds with kidney tissue and induce tissue injury and vascular endothelial damage. Salicylate is a glutathione depletor which limits the neutralization process of toxic acetaminophen metabolites.
- Analgesic nephropathy predominantly affects the medulla and papillary tip. Characteristic presentations include CKD, papillary necrosis and calcifications on computed tomography (CT), or small echogenic kidneys with irregular/lobulated contours on kidney ultrasound (**Figure 6.4**).

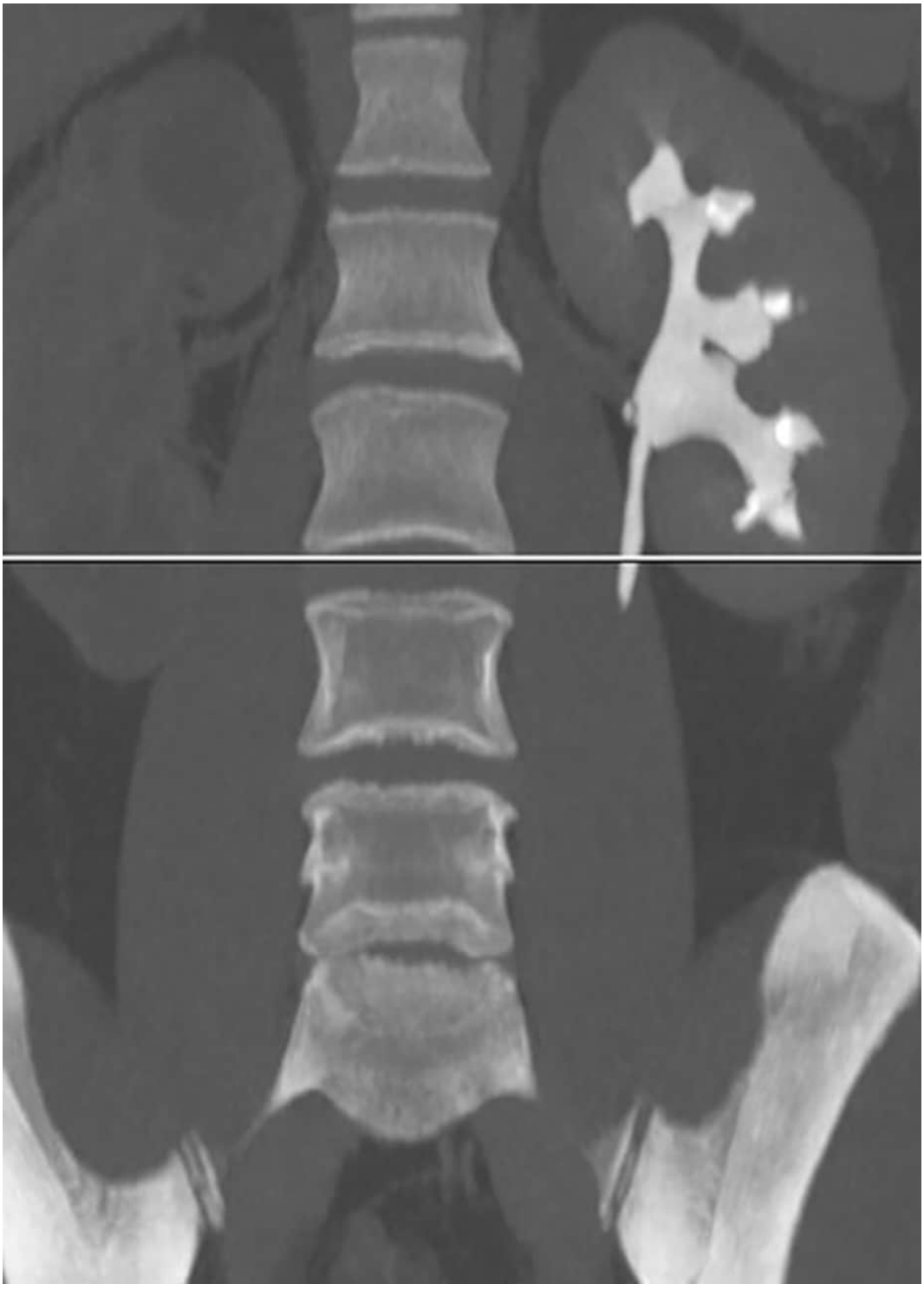


FIGURE 6.4 Papillary necrosis. Coronal postcontrast excretory phase maximum intensity projection images showing classic appearance of papillary necrosis.

- Single analgesic use may also lead to analgesic nephropathy.
  - Acetaminophen:
    - Nurses' Health Study (~1,700 healthy women), follow-up over 11 years: Greater than 3,000 g of acetaminophen gave an odds ratio of 2.04 for a

decrease in glomerular filtration rate (GFR) of greater than 30 mL/min/1.73 m^2 compared to less than 1,000 g use.
        - Physicians' Health Study (11,000 healthy men): no increased relative risk of CKD with exposure of 2,500 or more pills over a period of 11 years
    - Salicylates (aspirin): Most studies suggest that the long-term use of daily therapeutic aspirin dose alone without concurrent use of acetaminophen does not lead to kidney injury.
    - NSAIDs: High dose of NSAIDs may induce CKD in those with underlying or high risk for kidney injury but not in healthy individuals.
- Treatment: drug withdrawal and routine CKD management as needed

Proton pump inhibitors:

- More commonly reported in older patients, female predominance
- Tend to present as subacute rather than AIN (ie, slow rise in serum creatinine over months)
- Kidney biopsy shows interstitial nephritis ± granulomatous changes.

Lithium-induced kidney injury:

- Toxic intracellular lithium levels are thought to alter primary cilia function and lead to tubular cyst formation.
- Commonly associated glomerular lesions: global sclerosis, FSGS, minimal change disease
- Lithium may also be associated with nephrogenic diabetes insipidus, distal renal tubular acidosis (dRTA), hypercalcemia, and hypothyroidism.
- Histopathology (**Figure 6.5**): CIN/nephropathy with cortical and medullary distal tubular and collecting duct dilatations/cysts, tubular atrophy, and interstitial fibrosis with notable to minor interstitial inflammation and glomerular sparing or sclerosis

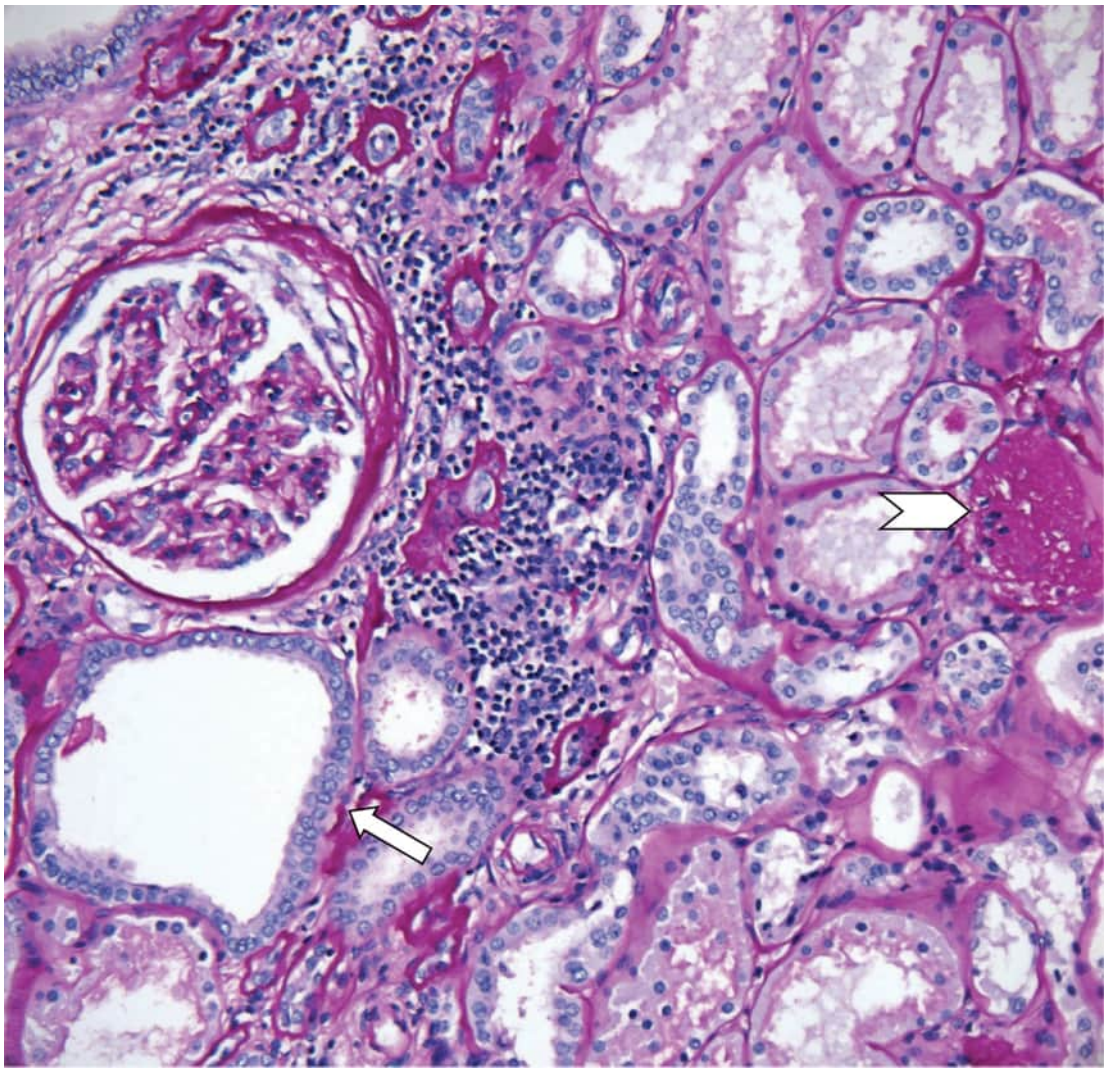


FIGURE 6.5 **Lithium-induced chronic interstitial nephritis.** There are focal tubular atrophy and interstitial fibrosis with associated lymphocytic inflammation. Microcystic dilatation of a distal tubule (left lower corner, arrow) and a globally sclerotic glomerulus (chevron) are also seen (periodic acid-Schiff ×200).

Tubular cysts may be evident on CT imaging.

- Management:
  - Discontinue lithium if safe and possible. Be aware, however, there are reports of patients committing suicide with lithium discontinuation.
  - Routine CKD management to slow GFR decline
  - Consider amiloride during lithium use to reduce its reabsorption at collecting tubules.
  - Thiazides may be considered in the treatment of nephrogenic diabetes insipidus.

Aristolochic acid (AA) nephropathy, aka Chinese herb nephropathy

- First reported in Belgium where the use of slimming regimens containing AA was used. Affected patients may develop rapidly progressive interstitial nephritis that can

progress to end-stage kidney disease (ESKD) due to high doses of AA in the herbal medications.

- Balkan nephropathy is also associated with AA, predominantly found in wheat. There is a much lower exposure to AA and progression to ESKD takes years to decades.
- Histopathology: progressive parenchymal scarring with variable interstitial inflammation, often appearing as a chronic interstitial nephropathy
- Associated with urothelial malignancy

Calcineurin inhibitors

- Clinical manifestations: typically presents as CKD, ± hyperkalemia, metabolic acidosis
- Histopathology: interstitial fibrosis and tubular atrophy in a striped pattern with minimal to no inflammation (chronic nephropathy). Often outer nodular arteriolar hyalinosis. Glomeruli may be normal or show FSGS and there may be enlarged juxtaglomerular apparatus.

Infection-related CIN (Table 6.2)

Table 6.2 Infection-related chronic interstitial nephritis

	Characteristics	Imaging & histology	Management
Emphysematous pyelonephritis	• ***Life-threatening necrotizing acute pyelonephritis*** +/− obstruction • Risk: DM • Common **gas-forming organisms**: *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Proteus mirabilis*	• Plain abdominal radiograph, ultrasound, or CT: presence of gas pockets • Histology: Interstitial nephritis may be present.	• Antibiotic specific to microorganism • Relief of obstruction • Surgical resection as needed
Xanthogranulomatous pyelonephritis (XGP)	XGP is ***associated with chronic obstruction*** (eg, staghorn calculi) and urinary tract infections.	• CT: ***low-density masses with calcifications resembling renal malignancy*** • Histology: diffuse cellular infiltrate of lipid-laden foam cells +/− granulomas and multinucleated giant cells	• Antibiotic specific to microorganism involved • Relief of obstruction • Surgical resection as needed
HIV immune restoration	• IRIS: ***disease or pathogen-specific inflammatory***	• Ultrasound: Kidneys may be	• Treat opportunistic infections,

	Characteristics	Imaging & histology	Management

inflammatory syndrome (IRIS)	***response*** *triggered after* ART initiation, reinitiation, or intensification/modification, or treatment of tuberculosis
	• Manifestation: worsening of an ongoing disease or unmasking of undiagnosed disease
		slightly enlarged due to acute inflammatory response.
		• Histology: ***chronic interstitial nephritis +/− granulomas***
			supportive care
			• Severe IRIS:
			  • Consider holding ART.
			  • Consider steroid if no cryptococcal meningitis or Kaposi sarcoma: Monitor for other opportunistic infections.

Malakoplakia	• Rare granulomatous disease of infectious origin due to defective macrophage function • Characterized by presence of ***MG bodies*** (lysosomes filled with partially digested bacteria +/− calcium and iron deposits)	• US/CT: ***mass-like lesions mimicking renal carcinoma*** • Histology: sheets of histiocytes with basophilic inclusions of concentric laminations (MG bodies) made of calcium and iron	• Surgical resection • Antibiotics (quinolones, trimethoprim-sulfamethoxazole, rifampicin)

Abbreviations: ART, antiretroviral therapy; DM, diabetes mellitus; MG, Michaelis-Gutmann; US/CT, ultrasound/computed tomography.

Emphysematous pyelonephritis (**Figure 6.6**):

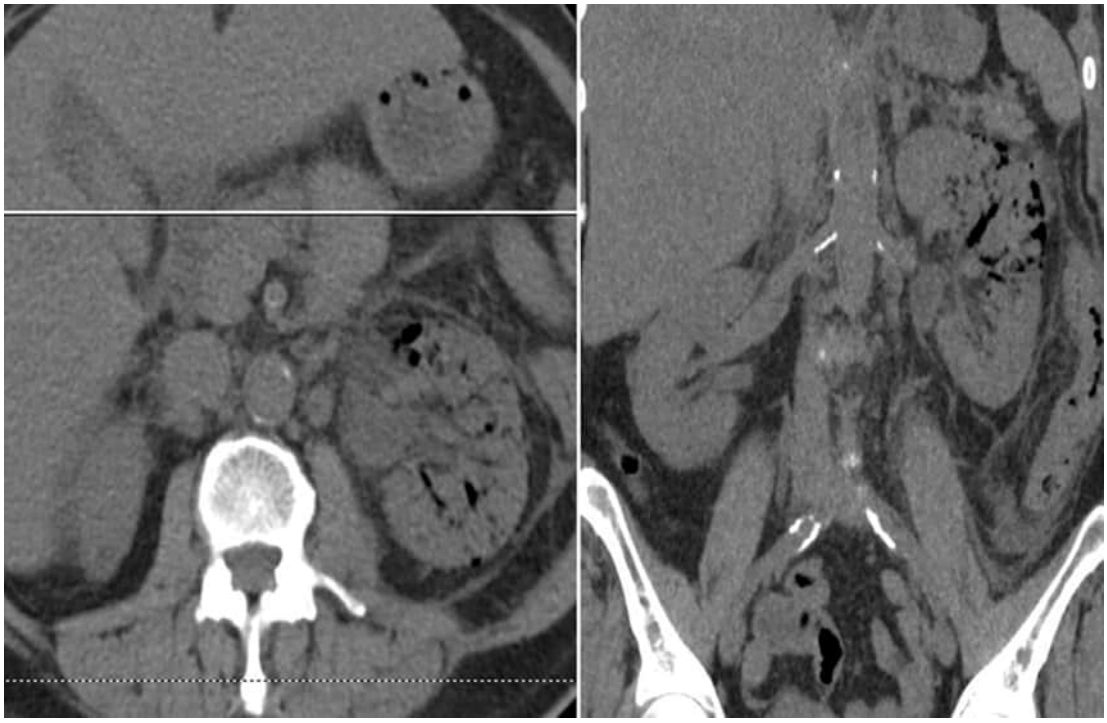
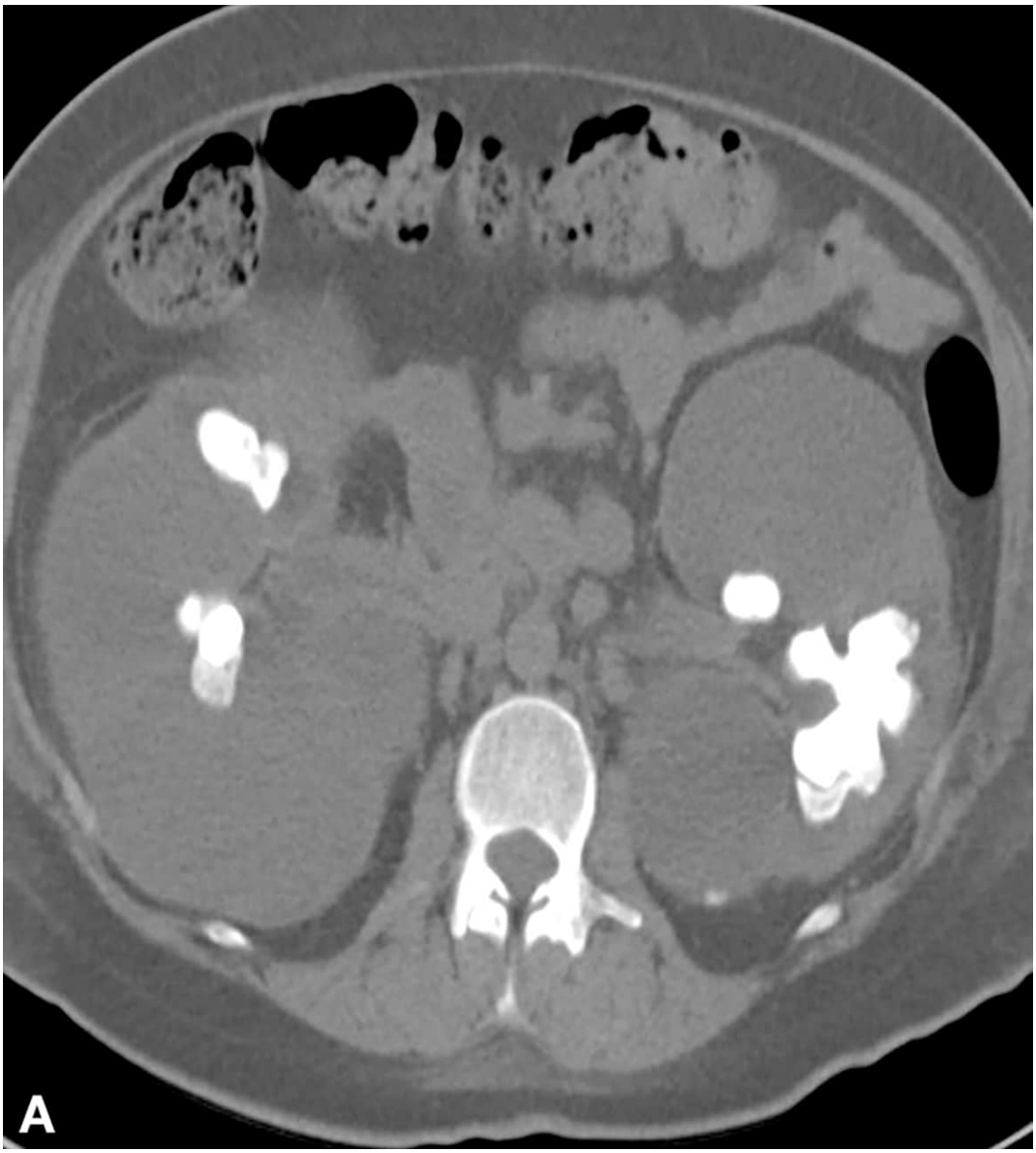


FIGURE 6.6 **Emphysematous pyelonephritis.** Axial and coronal noncontrast computed tomography images showing crescentic collection of gas within Gerota fascia (indicative of infection within the perinephric spaces) consistent with emphysematous pyelonephritis.

- Life-threatening necrotizing acute pyelonephritis
- Risks: diabetes mellitus and urinary obstruction
- Commonly caused by gas-forming organisms such as *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*
- Gas pockets may be detected on plain abdominal radiograph, ultrasound, or CT. Infection involving the pelvis only is called emphysematous pyelitis.
- Management: organism-specific antibiotics, relief of obstruction, drainage of abscess, and surgical resection as needed

Xanthogranulomatous pyelonephritis

- Condition associated with chronic obstruction (eg, staghorn calculi) and urinary tract infections with resulting granulomatous inflammation within the kidneys
- CT: low-density masses with calcifications (due to granulomatous inflammation enveloping a stone) mimicking renal malignancy; severe dilation of pelvis and calyces resulting in a multiloculated appearance resembling a bear paw, termed "bear paw sign" (**Figure 6.7**)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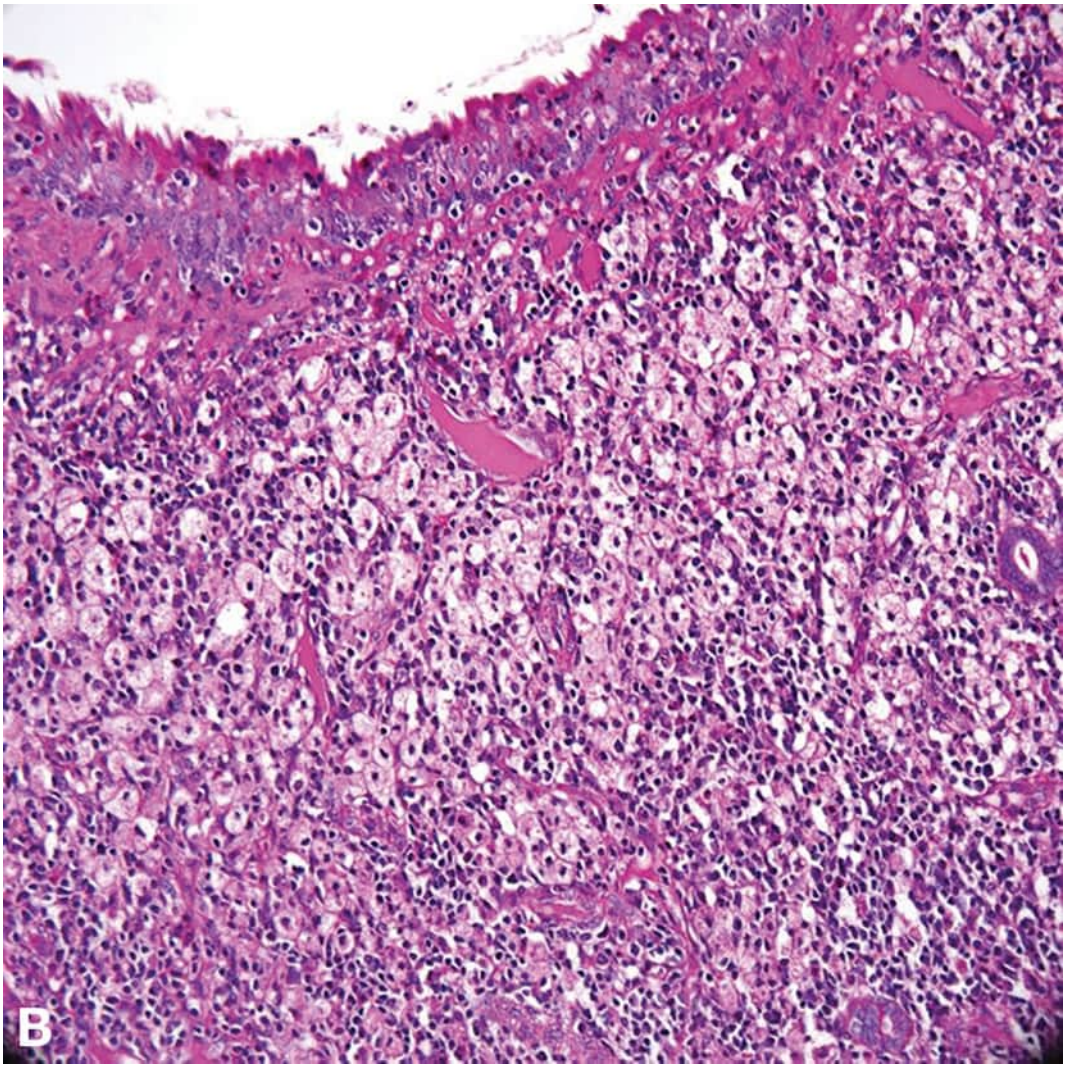


FIGURE 6.7 **Xanthogranulomatous pyelonephritis.** A. Coronal noncontrast computed tomography (CT) image showing enlarged kidneys containing staghorn calculi with resulting contraction of the renal pelvices and associated ballooning of the renal calyces and inflammation of the perinephric fat. The appearance of xanthogranulomatous pyelonephritis on CT has been compared to a "bear paw" with the ballooned renal calyces representing the paws. B. The renal pelvis and medulla are diffusely infiltrated with foamy (xanthomatous) cells, which are lipid-laden macrophages, and lymphocytes obliterating the normal renal parenchyma (hematoxylin and eosin ×200).

- Histology: diffuse infiltrate of lipid-laden foam cells (macrophages) replacing normal renal parenchyma with focal granuloma formation; presence of neutrophils with pyelonephritis
- Clinical manifestations: commonly affect middle-aged women who may present with fevers/chills, chronic flank pain, and possibly palpable mass
- Urine cultures may reveal *E. coli*, *Klebsiella, Proteus*, and, less often, *Staphylococcal species*.
- Prolonged disease can lead to secondary amyloidosis (AA amyloid) and nephrotic syndrome.

- Management: organism-specific antibiotics, relief of obstruction, surgical resection as needed

Malakoplakia:

- Rare granulomatous disease of infectious etiology (bacterial, fungal, tuberculosis, etc)
- Presents as friable yellow plagues that may involve genitourinary tract, GI tract, other visceral organs, skin (erythematous nodular lesions, ulcerations, fistulas/abscesses)
- Reported in immunocompromised hosts and patients with asthma
- Pathogenesis: thought to be due to defective macrophage function
- Diagnosis: urine culture and biopsy
- Imaging studies may reveal mass-like lesions, mimicking renal tumors.
- Histopathology (**Figure 6.8**)

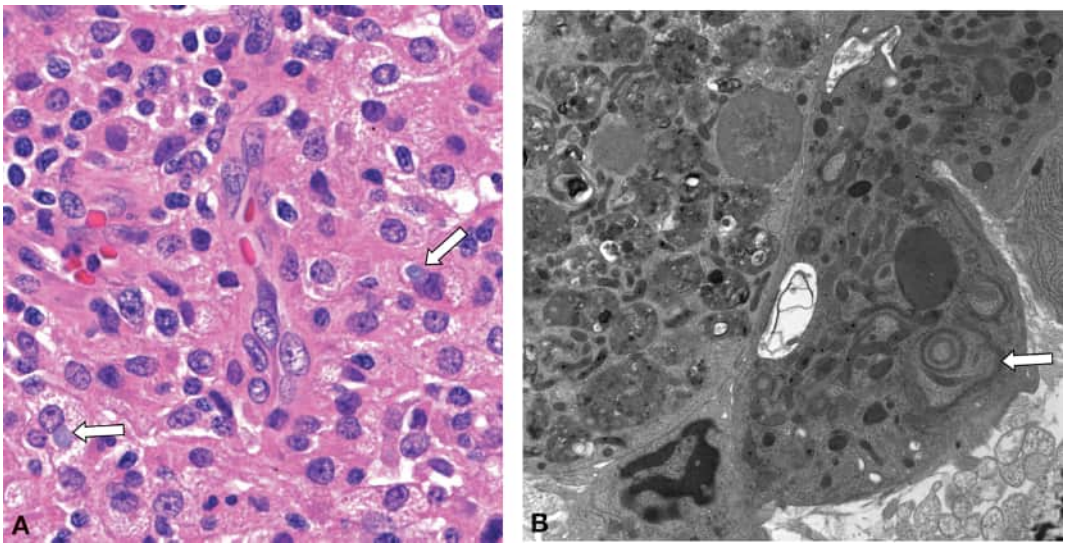


FIGURE 6.8 **Malakoplakia.** A. Interstitial macrophages with abundant granular cytoplasm containing rounded calcifications (Michaelis-Gutmann bodies, arrows) (hematoxylin and eosin ×600). B. Electron micrograph of a macrophage showing a forming calcospherule (Michaelis-Gutmann body, arrow ×12,000).

- Hematoxylin and eosin staining show sheets of histiocytes with basophilic inclusions of concentric laminations called Michaelis-Gutmann (MG) bodies. MG bodies are lysosomes filled with partially digested bacteria with calcium and iron deposits on bacterial glycolipids. MG bodies are considered pathognomonic for malakoplakia.
- EM: MG bodies consist of lysosomes filled with partially digested bacteria. Identification of the responsible organism may be possible with bacterial gram staining or immunostaining with antibody against *Mycobacterium bovis*, if such is the pathogenic organism.

- Management: surgical, antibiotics, for example, quinolones, trimethoprim-sulfamethoxazole, rifampicin

HIV immune restoration inflammatory syndrome (IRIS):

- IRIS refers to a disease- or pathogen-specific inflammatory response that may be triggered after antiretroviral (ART) initiation, reinitiation, or intensification/modification. IRIS may present as worsening of an ongoing disease (eg, ongoing opportunistic infection) or unmasking of an undiagnosed disease.
- IRIS may also be associated with the antituberculosis treatment of tuberculosis.
- Kidney involvement may manifest as interstitial nephritis ± granulomas.
- Treatment:
  - Treat opportunistic infections and provide supportive and symptomatic care.
  - ART should not be interrupted unless ongoing IRIS is life threatening.
  - Severe IRIS:
    - Consult infectious disease specialist regarding possibility of holding ART.
    - If IRIS is not caused by cryptococcal meningitis or Kaposi sarcoma, treat with 1 to 2 mg/kg prednisone or equivalent for 1 to 2 weeks followed by taper.
    - Monitor for the development of other opportunistic infections including CMV retinitis and tuberculous disease while receiving prednisone.

Heavy metal–associated CIN

Lead (Pb)

- Pathogenesis: chronic lead deposition and associated toxicity in proximal tubules, hyperuricemia, and hypertension (HTN)
- Clinical manifestations:
  - Chronic: anemia with basophilic stippling, gout, CKD, peripheral motor neuropathies, perivascular cerebellar calcifications, small shrunken kidneys
  - Acute lead intoxication: encephalopathy, abdominal pain, hemolytic anemia, Fanconi syndrome, and peripheral neuropathy
- Management: Pb chelation therapy

Mercury

- Found in alloy and mirror plants, batteries
- Mercury dichloride ($HgCl_2$) may induce CIN and acute tubular necrosis.

Cadmium

- Found in glass/metal alloy plants, electrical equipment
- Outbreak of cadmium toxicity in Japan due to industrial contamination led to itai itai, aka "ouch ouch" disease because of significant associated bone pain. Kidney involvement includes hypercalciuria, kidney stones, proximal tubular dysfunction, anemia, and CIN.

Arsenic

- Found in poison gas, insecticides, weed killers, paints

- Proximal RTA and CIN

IgG4-related disease

Pathogenesis

IgG4-RD is thought to be due to an inflammatory immune response triggered by an autoimmune process or presence of an infectious agent. The influx of inflammatory cells leads to multiorgan enlargement, cytokine release, eosinophilia, elevated IgG4 and IgE levels, and fibrosis of affected organs.

Patient characteristics

- Male predominance (60%-80%)
- Older age (>50 years)
- Up to 40% with history of allergic diseases (eg, bronchial asthma or chronic sinusitis)

Clinical manifestations

- A condition characterized by dense lymphoplasmacytic infiltration of predominantly IgG4-positive plasma cells and small lymphocytes in various organs
- Lymphoplasmacytic infiltration can lead to the formation of mass lesions in various organs including pancreas, autoimmune pancreatitis, enlarged (submandibular) salivary glands, kidneys (tubulointerstitial nephritis), lungs, lymph nodes, meninges, aorta (chronic sclerosing aortitis and periaortitis), breast, prostate, thyroid (thyroiditis), pericardium, skin, and even bone (destructive lesions resembling granulomatous polyangiitis).

Renal involvement: tubulointerstitial nephritis, membranous glomerulonephritis, IgG4-plasma cell arteritis, obstructive uropathy from retroperitoneal encasement/fibrosis

Clinical diagnosis

- Elevated serum IgG4 (~70%), hypocomplementemia (~50%), peripheral eosinophilia (~30%)
- Histopathology (**Figure 6.9**)

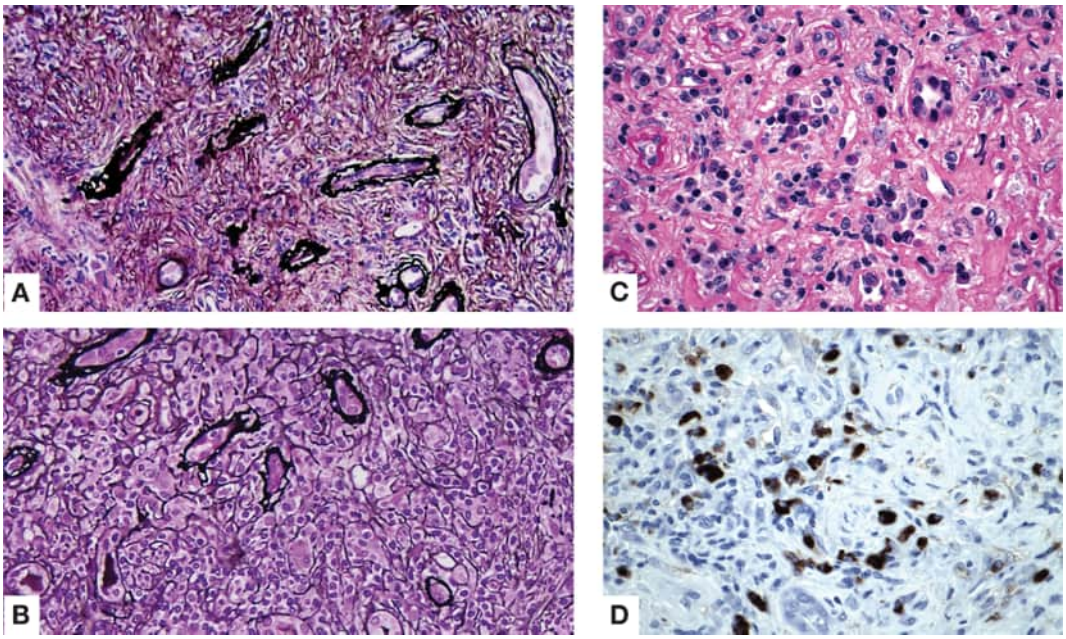


FIGURE 6.9 **IgG4-related disease.** A. There is interstitial fibrosis in a storiform (whirling) pattern with tubular atrophy and an interstitial inflammation (periodic acid methenamine silver ×200). B. Fibrosis surrounding individual and small clusters of inflammatory cells ("birds-eye" fibrosis) (periodic acid methenamine silver ×200). C. Small aggregates of lymphocytes and plasma cells (hematoxylin and eosin ×400). D. IgG4 immunohistochemical stain showing positive staining in more than 50% of the plasma cells and in more than 10 plasma cells in one 40× field (×400).

  - Dense lymphoplasmacytic infiltrates consisting of lymphocytes, plasma cells, eosinophils. Seeing greater than 10 IgG4+ plasma cells in one 40× field or a ratio of greater than 50% IgG4+/IgG4− plasma cells is highly suggestive of IgG4-RD.
  - The interstitial fibrosis typically has a "storiform" pattern, with a whorled pattern of fibrosis around mononuclear cell infiltrates ± eosinophils. Individual inflammatory cells may be encased in fibrosis ("birds-eye pattern").
  - Obliterative phlebitis, although rarely found on kidney biopsy
- Imaging: Abnormal findings such as organ enlargement, masses, perinephric stranding may be seen in more than 50% of patients.

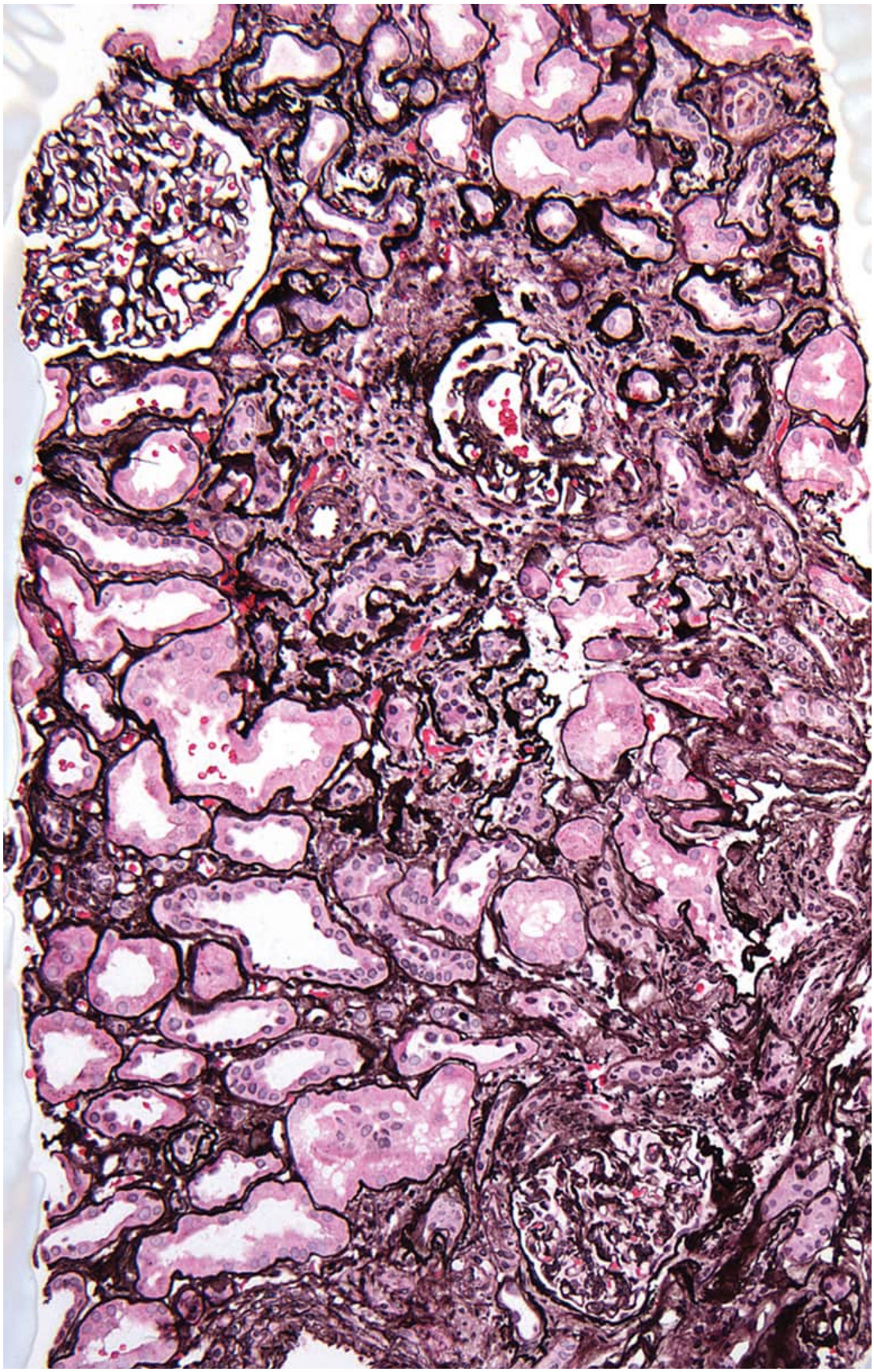
Treatment

- Glucocorticoids
  - Suggested regimen: prednisolone 0.6 g/kg body weight/d for 2 to 4 weeks, tapered over 3 to 6 months to 5 mg/d and maintain for up to 3 years
  - Response occurs even in the presence of severe interstitial fibrosis and tubular atrophy.
- Others: Rituximab, AZA, mycophenolate mofetil (MMF), and methotrexate have been suggested as GC-sparing agents.
- Relapse:
  - May be seen in up to 70%

- Predictors of relapse: elevated baseline serum IgG4, IgE, and circulating eosinophils

CKDu (CKD of unknown cause, Mesoamerican nephropathy, chronic interstitial nephritis in agricultural communities [CINAC])

- A nonproteinuric progressive form of CKD, originally described in agricultural workers in Central America in the absence of traditional risk factors such as HTN, diabetes, and glomerulonephropathies. Has been reported in other under-resourced agricultural communities around the world
- Contributing factors are thought to include (1) repeated exposures to severe dehydration with loss of body minerals such as sodium and potassium, consumption of sugar containing drinks leading to conversion of glucose to sorbitol and fructose with subsequent metabolism by fructokinase to oxidant mediators; (2) exposure to agrochemicals (fertilizers, pesticides, weed killers) via inhalation or skin absorption during unprotected spraying, ingestion of contaminated drinking water or food; (3) exposure to heavy metals, silica, arsenic, fluoride; (4) infections such as leptospirosis or hantavirus; (5) lifestyle exposures such as NSAIDs, herbal remedies, smoking, and (6) genetic predisposition.
- Typical manifestations: small kidneys with reduced cortical thickness on ultrasound, mild (tubular) proteinuria, hyperuricemia, hypokalemia
- Histopathology (**Figure 6.10**): interstitial fibrosis and tubular atrophy with minimal to moderate inflammation, enlarged glomeruli, periglomerular fibrosis, and mild vascular disease. In more advanced disease, there is prominent glomerulosclerosis, which may reflect glomerular ischemic injury. Large dysmorphic proximal tubular cell lysosomes frequently may be observed.



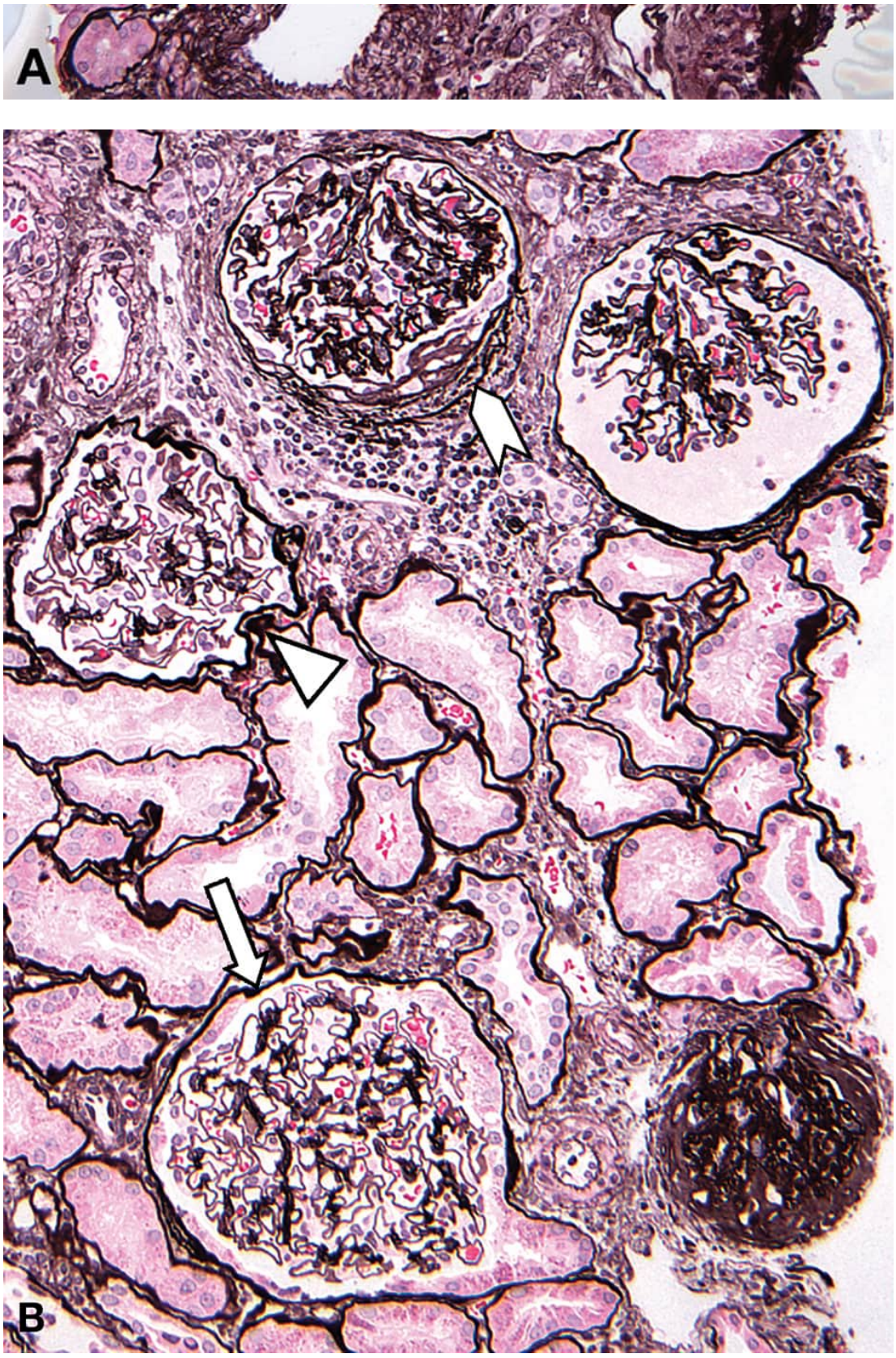

A
B

FIGURE 6.10 Chronic kidney disease of unknown etiology (CKDu). A. Focal interstitial fibrosis and tubular atrophy with minor inflammation (periodic acid methenamine silver ×100). B. Glomeruli showing mild enlargement (arrow), global sclerosis, ischemic-type wrinkling (arrowhead), and periglomerular fibrosis (chevron) (Periodic acid methenamine silver ×150). C. Large dysmorphic proximal tubular cell lysosomes containing dispersed electron dense aggregates frequently may be observed (×4,000).

Miscellaneous

Inflammatory bowel disease is associated with an increased risk of CIN, independent of exposure to 5-aminosalicylates.

Granulomatous (noncaseating) CIN

- Drugs: sulfas, synthetic penicillin, NSAIDs, thiazides, quinolones, PPIs, 5-aminosalicylate agents, intravesical BCG (Bacillus Calmette-Guérin) therapy, antiepileptics

- Infections: tuberculosis, leprosy, xanthogranulomatous pyelonephritis, histoplasmosis, glandular fever
- Systemic diseases: granulomatous polyangiitis, sarcoidosis, TINU, chronic lymphocytic leukemia, Crohn disease, primary biliary cirrhosis
- Others: urate, oxalosis, tubular rupture (due to obstruction, crystals)

Karyomegalic interstitial nephritis:

- Rare, most often adult-onset, slowly progressive
- Histopathology (**Figure 6.11**): tubular cells (predominantly proximal) with large bizarrely shaped nuclei and often attenuated cytoplasm
- Pathogenesis: autosomal recessive mutations in *FAN1* gene impairing DNA interstrand cross-link repair, medication induced (ifosfamide)
- Unknown treatment for genetic form. Medication-induced type may respond to drug discontinuation and steroids.

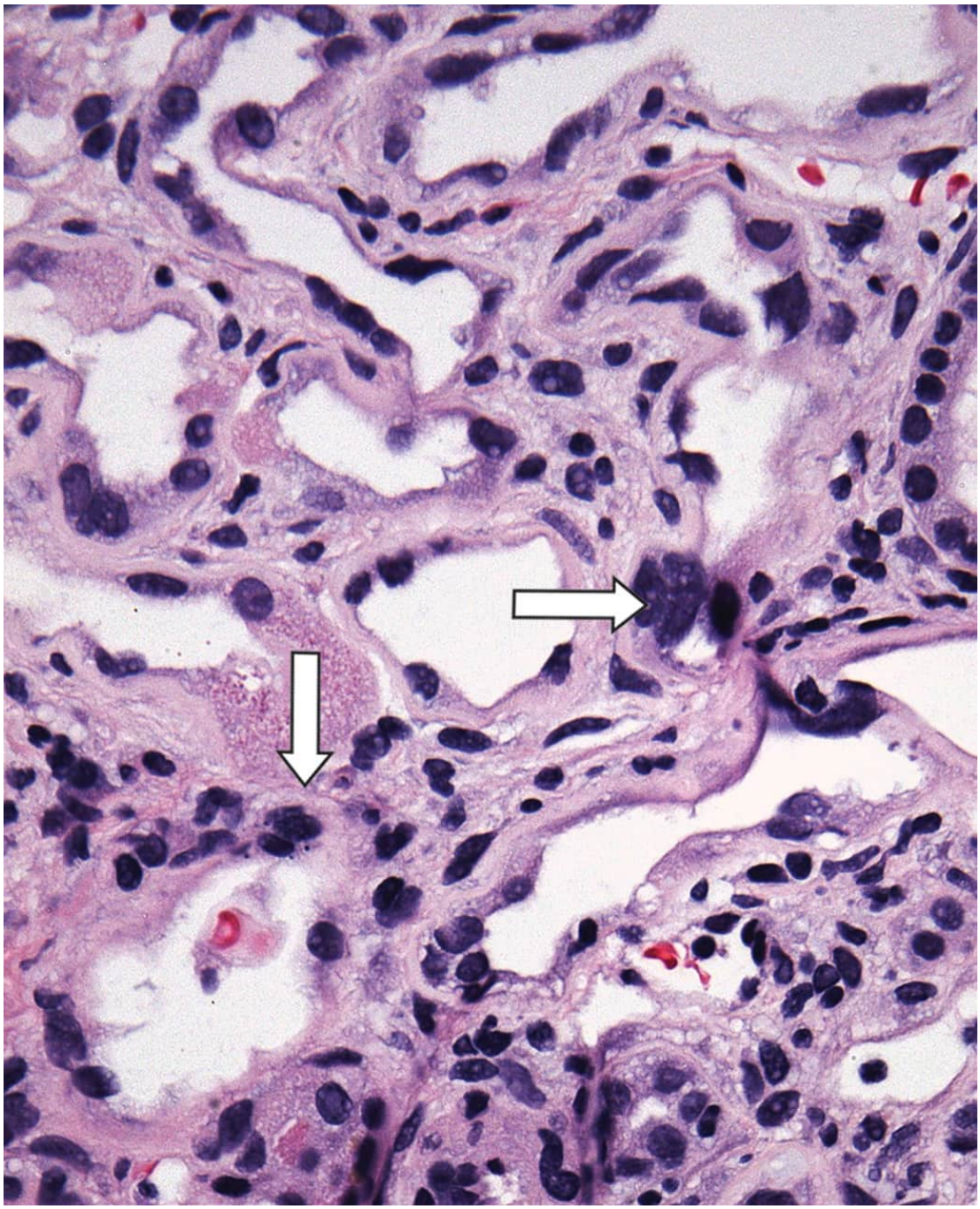


FIGURE 6.11 **Karyomegalic interstitial nephritis.** Large bizarrely shaped tubular cell nuclei (arrows) are found predominantly in proximal tubules, associated with markedly attenuated cytoplasm (H&E ×400).

RENAL CYSTIC DISEASES

Table 6.3 summarizes major renal cystic diseases.

Table 6.3 Cystic and chronic tubulointerstitial kidney diseases

Cystic kidney diseases without tumor associations		Cystic kidney diseases with tumor syndromes	Other cystic diseases	
AR chronic interstitial nephritis	**AD tubulointerstitial kidney disease**	**[a]Tuberous sclerosis complex**	**Multicystic dysplastic kidney disease**	**Simple cysts**
• Small kidneys ± corticomedullary cysts • [b]Also known as nephronophthisis • Associations: retinitis pigmentosa, liver fibrosis, situs inversus, bronchiectasis, polydactyly, neurologic abnormalities, volume depletion • ESKD by 30 years old is typical.	• Small kidneys ± corticomedullary cysts • Mutations: UMOD, MUC1, HNF1β, REN, or SEC61A1 • Associated findings: gout, hyperuricemia with UMOD and REN, anemia and volume depletion with REN • ESKD in adulthood	• Germline mutation: TSC1 (hamartin), TSC2 (tuberin), or both • Associations: hamartomas of brain (seizures, developmental delay), eyes, heart, lung, liver, kidney, skin • Kidneys: AML, cysts, RCC, LAM • Skin: angiofibromas, ash leaf spots, Shagreen patches	• Immature tubular cysts with disorganized kidney parenchyma in utero • Cysts typically involute; affected kidney atrophies with age • 30% have other CAKUT (eg, vesicoureteral reflux in contralateral kidney, neurogenic bladder, duplicating collecting system, ectopic kidneys). • Complications: FSGS, albuminuria	• Typically simple cysts are asymptomatic, solitary, and unilateral. • Large cysts may be associated with HTN and erythrocytosis. • Cyst growth rate is not affected by transplantation, whether it is in the donor or recipient.
Medullary sponge kidney		von Hippel-Lindau syndrome	Benign (multifocal) cystic nephroma	Acquired cystic kidney disease
• Mostly sporadic • Dilation of terminal collecting ducts in medullary papillae with normal size kidneys • Characteristic imaging study: abdominal radiograph showing radiopaque concretions of calcium stones; excretory urography with contrast retention in dilated collecting ducts in medullary papillae resembling "flower bouquets" or "paintbrush" • Associated with nephrocalcinosis, calcium stones, distal RTA, hypocitraturia • Complications: urinary tract infections and obstruction • Typically benign but may have CKD due to recurrent urinary tract infections		• Germline mutation: VHLp • Associations: RCC, retinal or CNS hemangioblastomas, pheochromocytomas, pancreatic or endolymphatic sac tumors, renal and pancreatic cysts, epididymal or broad ligament cystadenomas • Normal kidney size with small number of small cysts. All cysts are potentially preneoplastic.	• Benign mixed mesenchymal and epithelial neoplasm • Typically Bosniak III, well-circumscribed cystic mass, often indistinguishable from RCC • Bimodal age: <4-year-old boys and postmenopausal women	• Associated with CKD • Risks: dialysis vintage • May have associated malignancy • Histology: cysts in all nephron segments, tubular cell hypertrophy and hyperplasia • Screening in patients with advanced CKD

Cystic kidney diseases without tumor associations	Cystic kidney diseases with tumor syndromes	Other cystic diseases	
and obstruction		• Generally benign but RCC is possible. • Management: surgical resection	G5D and G5T is recommended. • ACKD may also be associated with chronic hypokalemia.
AR polycystic kidney disease	Birt-Hogg-Dube syndrome	Glomerulocystic kidney disease	
• Mutation of PKHD1 (fibrocystin/polyductin) • Fusiform saccular dilation of collecting ducts and remodeling of biliary system • Histology: dilated collecting ducts radially arrayed perpendicular to the capsule, extending from medulla to cortex • Striated nephrogram on CT • Complications: hepatic fibrosis, ascending cholangitis, cholangiocarcinoma • ESKD in 60% by age 10	• [c]Germline mutation: FLCN (folliculin) • Associations: fibrofolliculomas (white popular lesions on nose, cheeks), pulmonary cysts • RCC only occurs if there is also a somatic mutation of the normal copy of FLCN.	• Familial or sporadic • Cystic dilatation of Bowman space and occasionally S1 proximal tubules • Ultrasound: increased echogenicity of cortex with minute cysts • May be associated with RCC	
AD polycystic kidney disease			
• Mutation of PKD1, PKD2, GANAB, and others • PKD1 present with more cysts, larger kidneys, worse prognosis compared with PDK2. • Moderately to massively enlarged kidneys • Histology: Cysts in all parts of the nephron • Associations: liver cysts, aneurysms, stones (uric acid			

Cystic kidney diseases without tumor associations	Cystic kidney diseases with tumor syndromes	Other cystic diseases	
and calcium oxalate), mitral and aortic valve prolapse, diverticulosis, HTN • Treatment: tolvaptan			

Abbreviations: ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AML, angiomyolipoma; AR, autosomal recessive; CAKUT, congenital abnormality of the kidney and urinary tract; CCB, calcium channel blocker; CIN, chronic interstitial nephritis; CKD, chronic kidney disease; CNS, central nervous system; CT, computed tomography; dRTA, distal renal tubular acidosis; ESKD, end-stage kidney disease; FDA, U.S. Federal Drug Administration; FSGS, focal segmental glomerulosclerosis; G5D, CKD stage 5 on dialysis; G5T, CKD stage 5 in transplant recipients; HNF1β, gene encoding hepatic nuclear factor 1b; HTN, hypertension; LAM, lymphangioleiomyomatosis; MUC1, gene encoding mucin 1; RCC, renal cell carcinoma; REN, gene encoding prorenin; SEC61A1, gene encoding the a1 subunit of SEC61 translocon pore; UMOD, gene encoding uromodulin; UTI, urinary tract infection; TSC, tuberous sclerosis complex; VHLp, von Hippel-Lindau protein.

[a]TSC/PKD1 continuous gene syndrome also belongs to syndromes with kidney tumors.

[b]Nephronophthisis is previously known as medullary cystic kidney disease.

[c]In BHD, pulmonary cystic disease and fibrofolliculomas may occur without the somatic mutation, but RCC requires somatic mutation of the second FLCN copy.

Multicystic Dysplastic Kidney Disease (Renal Dysplasia) (MCDK)

Background

- MCDK is a nonhereditary renal cystic condition involving a **C**ongenital **A**bnormality of the **K**idney and **U**rinary **T**ract (**CAKUT**) where irregular cysts of various sizes replace the normal renal cortex, leading to a nonfunctional kidney.
- MCDK is typically a unilateral disease but may involve both kidneys.
- The incidence of MCDK is less than 0.1% with a male predilection over female of 1.3 to 1.9:1 ratio.

Pathogenesis

- Known mutations account for less than 20% of cases and predominantly include genes involved in glomerular development, ureteric branching, and metanephric mesenchyme.
- May be seen with fetal alcohol syndrome

Clinical manifestations

- Age of onset: in utero, may present with oligohydramnios
- 30% of patients have other CAKUT: vesicoureteral reflux in contralateral kidney, neurogenic bladder, duplicating collecting systems, ectopic kidney
- Ultrasound: typically, only involves one kidney which may be seen as an enlarged kidney in utero due to multiple cysts without normal renal parenchyma.

Spontaneous involution with cystic collapse may occur in utero. Higher rate of involution by 10 years is seen with kidney size of less than 5 cm and more commonly for right than left kidney. Adults may present with one atrophic kidney and a single functioning kidney (may be confirmed with renal nuclear scan).

- Histopathology: disorganized kidney parenchyma with often cystically dilated immature tubules/collecting ducts surrounded by primitive mesenchyme, may have fetal cartilage
- MCDK is not associated with HTN or malignancy.

Management

Long-term follow-up for vesicoureteral reflux, albuminuria, and kidney injury is recommended.

Hereditary Tubulointerstitial Disease

Mode of inheritance may be autosomal dominant or recessive.

Autosomal dominant tubulointerstitial kidney disease (ADTKD)

- ADTKD is previously known as medullary cystic kidney disease.
- ADTKD is a rare kidney disease characterized by tubular damage and interstitial fibrosis with normal glomeruli that progresses to ESKD in adulthood.
- Subclassification of ADTKD is based on specific gene mutation involving UMOD, MUC1, REN, HNF1B, or SEC61A1.
- Histopathology: nonspecific interstitial fibrosis and tubular atrophy out of proportion to chronic vascular or glomerular disease, with or without tubular cysts, and with minor inflammation

Epidemiology

- Not accurately determined given rarity and underrecognition of disease
- Prevalence estimated to be 0.3% to 1% of patients with CKD stages 3 to 5 and 2% of patients with ESKD have ADTKD-UMOD.

Clinical manifestations common to ADTKD subtypes

- Small kidneys with or without corticomedullary cysts
- Renal insufficiency, bland urine
- ESKD by third decade of life with UMOD and sixth decade of life with MUC1 mutations
- Hyperuricemia and gout may be seen, particularly in ADTKD-UMOD and ADTKD-REN.
- HTN is uncommon prior to ESKD. As this is a chronic tubulointerstitial disease with concentrating defects, these patients tend to have volume depletion.
- Medullary cysts may be seen on ultrasound but are not present in most cases.
- Genetic testing is indicated for living related kidney donors.

ADTKD-UMOD subtype—most common subtype of ADTKD

- Mutation of UMOD, encoding uromodulin, also known as Tamm-Horsfall glycoprotein. Mutated uromodulin proteins are trapped in tubular epithelial cells, which lead to tubular cell apoptosis, reactive interstitial fibrosis, and cyst formation.
- ADTKD-UMOD is associated with defective function of thick ascending limb of Henle loop, salt wasting, volume depletion, hyperuricemia, gout, and ESKD early in the third to seventh decade of life.

ADTKD-MUC1 subtype

- Mutation of MUC1, encoding Mucin-1, which normally functions to protect epithelial mucus barrier and maintain immunomodulatory properties and signal transduction.
- ADTKD-MUC1 may present with ESKD by the sixth decade of life.

ADTKD-HNF1β-subtype

- Mutation of HNF1β encoding the hepatocyte nuclear factor-1β, a transcription factor involved in the early development of neural tube, lung, kidney, and GI and genital tracts
- ADTKD-HNF1β is associated with maturity-onset diabetes mellitus of the young type 5, renal cyst, hypomagnesemia, hypokalemia, and hypocalciuria. The latter is via reduction in calcium sensing receptor and claudin 19 and 10b.

ADTKD-REN subtype

- Mutation of REN, encoding preprorenin. Mutated preprorenin results in defective translocation to endoplasmic reticulum (ER) and lysozymes for processing into renin. Cytoplasmic accumulation of preprorenin in renin-producing cells leads to tubular dilation and fibrosis.
- ADTKD-REN is associated with anemia, hyporenin, hypovolemia, early onset hyperuricemia, and gout.
- Treatment with high salt diet or fludrocortisone may be indicated in symptomatic patients.

ADTKD-SEC61A1 subtype (most rare of all ADTKD)

- Mutation of SEC61A1, encoding the α1 subunit of SEC61 translocon pore: The translocon complex mediates transport of signal peptide-containing precursor polypeptides across the ER.
- ADTKD-SEC61A1 is associated with dysplastic kidneys ± simple cysts, congenital anemia, intrauterine or postnatal growth retardation, neutropenia, recurrent cutaneous abscesses.

Management common to all ADTKD

- No specific treatment: Follow guidelines established for the management of CKD.
- Consider losartan and/or xanthine oxidase inhibitors in patients with gout.
- Use diuretics with caution due to the potential for volume depletion and hyperuricemia.
- Low salt diet is not recommended given concerns for potential volume depletion.

- Anemia and hypotension/hyperkalemia may be treated with erythropoiesis-stimulating agents and fludrocortisone, respectively.

Autosomal recessive tubulointerstitial disease, aka nephronophthisis (NPHP)

NPHP is characterized by urinary concentrating defects, chronic tubulointerstitial nephritis, cyst formation, and progression to ESKD, typically by the age of 30. NPHP is classified based on the age of onset as infantile, juvenile, or adolescent.

Epidemiology

- One of the most common genetic disorders leading to ESKD in children
- Accounts for 2.4% to 15% of ESKD in this age group

Pathogenesis

- Responsible genes are those encoding nephrocystin proteins involved in the function of primary cilium, basal body, and centrosome in tubular epithelial cells.
- Mutations of more than 25 different genes have been implicated.
- Causal genes are not known in 2/3 of NPHP cases.

Clinical manifestations

- Age of onset: In utero but age of symptom onset depends on specific mutated NPHP gene.
- Polyuria, polydipsia requiring fluid intake at night, secondary enuresis, anemia, growth retardation, may be hyperuricemia
- Extrarenal manifestations reflecting a ciliopathy syndrome occur in 10% to 20% of cases and include retinal defects (retinitis pigmentosa, ocular apraxia, nystagmus, coloboma), liver fibrosis, cardiac malformation, situs inversus, bronchiectasis, ulcerative colitis, skeletal abnormalities (polydactyly), and neurologic abnormalities (encephalocele, vermis aplasia, hypopituitarism).
- ESKD by the third decade of life but may range from the first few years to the fifth decade of life depending on the affected gene
- Ultrasound findings are similar to those seen in ADTKD: Kidneys are small to normal size with increased echogenicity and loss of corticomedullary differentiation. Corticomedullary or medullary cysts may be present. Thin section CT may identify corticomedullary cysts.
- Histopathology (**Figure 6.12**): TBMs with thick and thin areas showing multilayering on EM, tubular atrophy with cystic dilatation and irregular branching, variable interstitial fibrosis and inflammation, periglomerular fibrosis

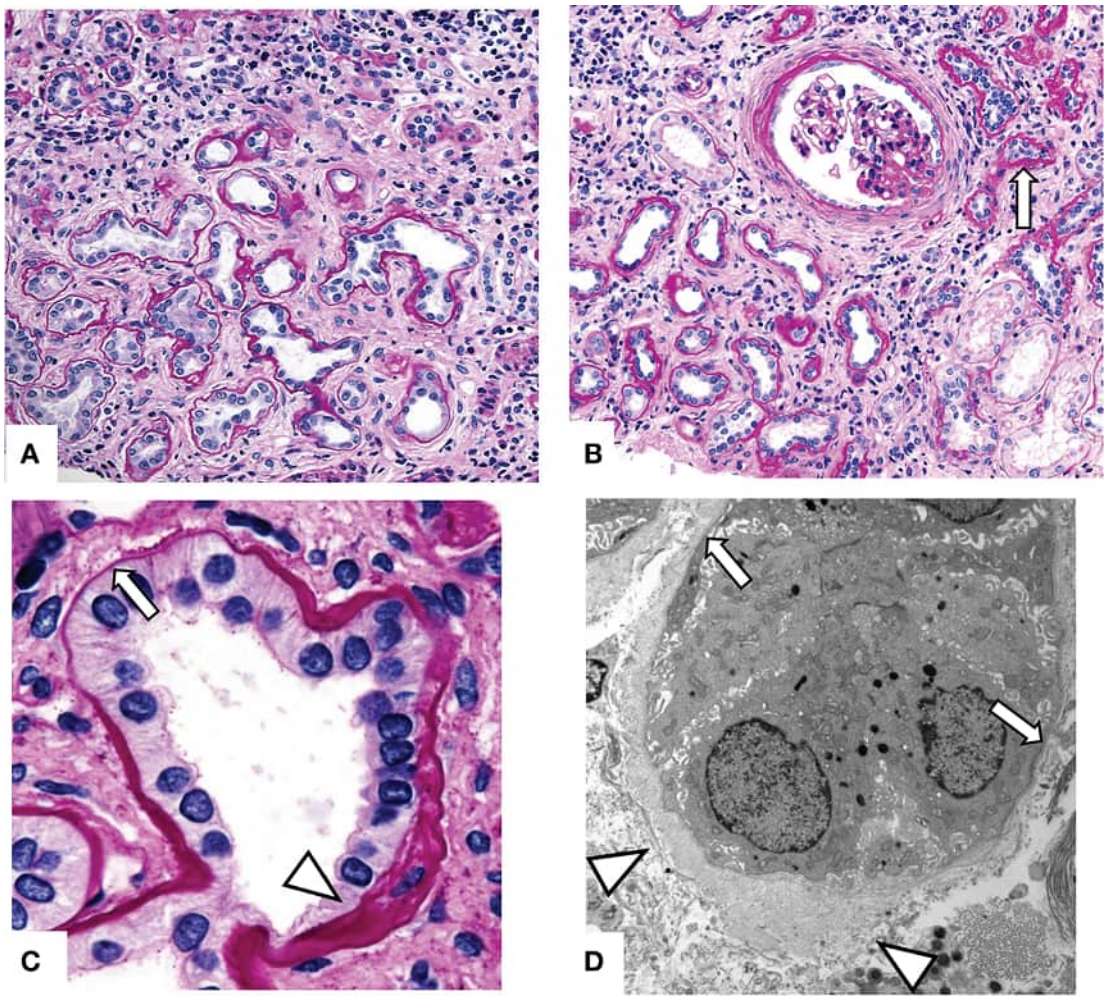


FIGURE 6.12 **Nephronophthisis.** A. Irregularly shaped tubules with variably thick and thin basement membranes, early tubular atrophy and mild interstitial inflammation and periglomerular fibrosis (periodic acid-Schiff ×150). B. Variably thickened tubular basement membranes with focal established tubular atrophy (arrow) and periglomerular fibrosis (periodic acid-Schiff ×150). C. Irregularly shaped tubule with segmental thin (arrow) and thickened multilayered (arrowhead) basement membrane (periodic acid-Schiff ×600). D. Electron micrograph showing thin (arrows) to thickened and layered (arrowheads) foci of the tubular basement membrane in a single tubule (×6,000).

Diagnosis

- Presence of clinical syndrome and genetic testing
- Genetic testing may be performed but a causative single-gene mutation is detected in only up to 60% of cases depending on the composition of the cohort studied.

Management

- No specific treatment: Follow guidelines established for the management of CKD.
- Consider salt, fluids, with or without fludrocortisone if hypotension/hypovolemia.

POLYCYSTIC KIDNEY DISEASES (PKDS)

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Factors implicated in the pathogenesis of ADPKD:

- Full or partial loss of functional polycystin (PC)

and either

- Somatic inactivation of the normal PKD allele and/or presence of mutated modifier genes leading to defective processing of PC or an imbalance in the expression of PC. This is known as the "second hit" theory.

or

- The level of functional PC is below a "critical threshold," that is, less than 10% to 30% within a tubular cell. It is thought that not all tubular cells are affected.
- Despite having large-sized kidneys, ADPKD cysts only involve less than 1% to 2% of all nephrons.

Gene mutations

- Gene mutations in ADPKD predominantly involve PKD1 and PKD2.
- PKD1 and PKD2 encode for polycystin PC1 and PC2, respectively. Relative frequencies of PKD1 and PKD2 mutations in genetically identifiable cases of ADPKD are approximately 85% and 15%, respectively.
- Mutations involving posttranslational processing of PC have also been reported to give rise to ADPKD. These may include GANAB, ALG9, and DNAJB11 genes (see **Appendix A6.2**). Seven percent to 10% of all ADPKD cases are genetically unresolved.
- Family history may be absent in 10% to 15% of patients with ADPKD due to de novo mutations, mosaicism, mild disease from PKD2, nontruncating PKD1 mutations, or misdiagnosis.

Epidemiology

- Incidence has been estimated to be 1 in 1,000 live births.
- ADPKD affects both genders and all ethnic groups equally.
- ADPKD accounts for 5% to 10% of patients with ESKD and is the fourth leading cause for kidney replacement therapy worldwide.

Pathogenesis (Figure 6.13)

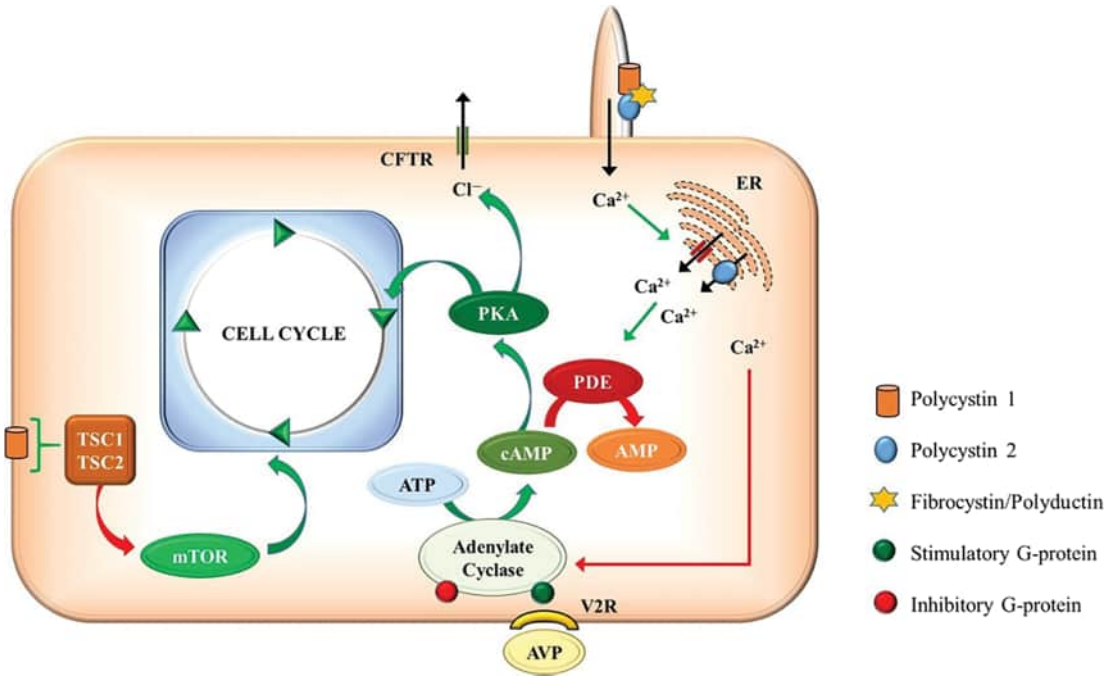


FIGURE 6.13 **Pathogenesis of autosomal dominant polycystic kidney disease.** PC1and PC2 form a polycystin complex on primary cilium on the apical surface of renal tubular and biliary epithelial cells. The normal PC complex functions as a mechanosensor that regulates flow-mediated Ca^{2+} entry into cells, which in turn triggers Ca^{2+} release from the ER into the cytoplasm. PC2 is also present in the ER, where it interacts with inositol triphosphate and ryanodine receptors to signal ER Ca^{2+} release into the cytoplasm.

Mutations of PC1 or PC2 interfere with flow-mediated increase in cytoplasmic Ca^{2+} level which leads to accumulation of cAMP. *(Intracellular cAMP level is determined by the net activity of adenylyl cyclase [AC] and phosphodiesterase [PDE]. Whereas AC increases cAMP production, and PDE breaks down cAMP. High intracellular* Ca^{2+} *activates PDE and inhibits AC. In the case of low intracellular* Ca^{2+} *associated with PC1 or PC2 mutation, AC activity is stimulated while PDE is inhibited, thereby favoring cAMP accumulation.)*

cAMP activates PKA.

PKA stimulates chloride-driven fluid secretion into the lumen of formed cysts by the phosphorylated CFTR and, in the presence of low intracellular Ca^{2+}, PKA promotes cellular proliferation.

Vasopressin binding to its receptor V2R increases cAMP levels via activation of AC.

PC1 on the cell surface also interacts with tuberin (TSC1). A disrupted PC1-TSC1 interaction causes a loss of downstream inhibition of mTOR. Uninhibited or unregulated mTOR activity leads to increased protein synthesis and cell proliferation.

Mutations involving fibrocystin/polyductin are associated with autosomal recessive polycystic kidney disease.

All green arrows and red arrows indicate stimulatory and inhibitory activities, respectively. Black arrows indicate the direction of electrolyte movement.

Abbreviations: AMP, adenosine monophosphate; ATP, adenosine triphosphate; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ER, endoplasmic reticulum; mTOR, mammalian target of rapamycin; PDE, phosphodiesterase; PKA, phosphokinase A; TSC1/TSC2, hamartin/tuberin complex; V2R, vasopressin receptor 2.

Mutations involving PC1

- PC1 is a membrane protein that involves protein-to-protein, cell-to-cell, and cell-to-matrix interactions, and intracellular signaling pathways necessary for normal cell

proliferation and survival. Mutations involving PC1 cause dysregulated cell proliferation and cyst formation.

- PC1 on the cell surface also interacts with tuberin. A disrupted tuberin-PC1 interaction causes a loss of downstream inhibition of the mammalian target of rapamycin (mTOR). Uninhibited mTOR activity leads to increased protein synthesis and cell proliferation.

Mutations involving PC2

- PC1 and PC2 form a PC complex on primary cilium on the apical surface of renal tubular and biliary epithelial cells. The normal PC complex functions as a mechanosensor that regulates flow-mediated calcium entry into cells, which in turn triggers calcium release from the ER into the cytoplasm, a process known as "*calcium-induced calcium release*." PC2 is also present in the ER, where it interacts with inositol triphosphate and ryanodine receptors to signal ER calcium release into the cytoplasm.
- Mutations of either PC1 or PC2 interfere with flow-mediated increase in cytoplasmic calcium level which leads to accumulation of cyclic adenosine monophosphate (cAMP), an important mediator of cystic growth. *(Intracellular cAMP level is determined by the net activity of adenylyl cyclase 6 [AC6] and phosphodiesterase-1 [PDE1]. Whereas AC6 increases cAMP production, PDE1 breaks down cAMP. High intracellular calcium activates PDE1 and inhibits AC6. In the case of low intracellular calcium associated with PC1 or PC2 mutation, AC6 activity is stimulated while PDE1 is inhibited, thereby favoring cAMP accumulation.)*
  - cAMP activates protein kinase A (PKA), which stimulates chloride-driven fluid secretion into the lumen of formed cysts by the phosphorylated cystic fibrosis transmembrane conductance regulator (CFTR). In addition, in the presence of low intracellular calcium, PKA promotes cellular proliferation via a multistep signaling pathway.
  - The proliferative effect of cAMP may be enhanced by epithelial growth hormone-like factors present in cystic fluid.
- Vasopressin (ADH [antidiuretic hormone]) can increase cAMP levels via activation of adenylate cyclase AD6 and promote cystic growth in individuals affected with ADPKD.

Diagnosis

Renal ultrasound diagnostic criteria for "at-risk individuals" for ADPKD

"At-risk individuals" is defined as individuals with first-degree relative of an index case with unknown genotype.

- 15 to 39 years old: three or more cysts unilateral or bilateral
- 40 to 59 years old: two or more cysts in each kidney
- 60 years or above: four or more cysts in each kidney
- If positive family history, in utero presence of even one cyst confirms the diagnosis.

- In the United States, presymptomatic screening for at-risk children is not recommended.

Criteria for disease exclusion in "at-risk individuals"

- Ultrasound based:
  - 30 years old or above: no cyst
  - 40 years old or above: less than two renal cysts
  - Absence of cyst by ultrasound in individuals younger than the age of 30 does not exclude ADPKD with certainty.
- MRI is better than ultrasound for excluding ADPKD in individuals <40 years old. Having less than 5 cysts on MRI in individuals <40 years old exclude ADPKD.
- Obtain direct DNA sequencing for potential kidney donors at risk for ADPKD and aged below 40 years.

Genetic diagnosis

- Genetic diagnosis is reserved for atypical presentations of ADPKD (eg, unilateral involvement or marked asymmetric disease, kidney failure without significant kidney enlargement), definitive diagnosis in a potential kidney donor, or reproductive counseling.
- Preimplantation genetic diagnosis is available for ADPKD.
- There are no established imaging-based criteria for diagnosis of ADPKD in patients without a family history. Some experts suggest the diagnosis of ADPKD if there are 10 or more cysts of greater than 5 mm in each kidney, particularly in the presence of enlarged kidneys or liver cysts. Genetic testing may be considered in equivocal cases.

Clinical manifestations

- PKD1 have more cysts and larger kidneys compared with PKD2. Cystic growth rates are similar between PKD1 and PKD2. The lower number of cysts, aka "lower cyst dose," in PKD2 is thought to result in later development of ESKD in PKD2 compared with PKD1.
- Clinical findings from the Consortium for radiologic imaging studies of ADPKD (**CRISP**):
  - The value of MRI in the study of ADPKD:
    - Cyst volume increase may be detected within 6 months.
    - Renal blood flow may be used as a marker of disease severity. The decline in kidney function and disease progression of ADPKD appears to be closely linked with the decline in renal blood flow.
  - PKD1 is a more severe disease compared to PKD2 because, in PKD1, more cysts develop earlier rather than growing faster.
  - Cystic growth with an increase in total kidney volume (TKV) is a continuous and steady process that is patient specific. At 3-year follow-up, the mean annual growth rate was 5% to 6%.

- Histopathology (**Figure 6.14):** Cysts occur in all parts of the nephron (Bowman space to collecting ducts) with variable sizes and shapes, without epithelial cell hyperplasia. Glomerular tufts are typically preserved despite cystic Bowman space dilatation.
- GANAB mutations are associated with autosomal polycystic liver disease and mild ADPKD with few renal cysts. Liver involvement ranges from having no cyst to severe polycystic liver disease requiring surgical intervention.

FIGURE 6.14 **Autosomal dominant polycystic kidney disease.** Kidney showing variably sized cysts in the cortex and medulla involving all segments of the nephron, resulting in an indistinguishable corticomedullary junction.

Complications of ADPKD

End-stage kidney disease:

- ADPKD is the most common genetic cause of ESKD in adults.
- Prevalence of ESKD due to ADPKD is 5% to 10% in the dialysis population.
- PKD1 typically reaches ESKD by the fourth and PKD2 by the sixth decade of life.
- Risks for CKD progression:
  - TKV greater than 600 mL/m height or kidney length greater than 17 cm likely progress to stage 3 CKD within 8 years. See **Appendix A6.3** for TKV calculation.
  - Albuminuria
  - HTN (particularly if onset prior to age 35)
  - Male gender
  - Low birth weight
  - Higher plasma copeptin level (hence vasopressin) is associated with higher TKV and urinary albumin excretion and reduced GFR and effective renal blood flow.
  - Others: sickle cell trait, dyslipidemia

Kidney stones

- Stones may occur in approximately 20% of patients with ADPKD.
- Cyst burden (high TKV) is associated with hematuria and nephrolithiasis.
- Uric acid and calcium oxalate stones are most common in ADPKD.
- Increased stone risk is thought to be due to urinary stasis from cyst compression, low urinary pH presumably due to defective ammonium excretion, hypocitraturia, and hyperuricosuria.

Hypertension

- Occurs even prior to reduction in GFR in 60% of patients
- Absence of nocturnal blood pressure (BP) dipping is common (in 40% of patients).
- Implicated underlying etiologies:
  - Activated renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system due to cyst compression and associated renal parenchymal hypoxia
  - Impaired vascular tone
  - Others: increased circulating endothelin-1, erythropoietin, vasopressin, insulin resistance

Cardiovascular system

- Left ventricular hypertrophy
- Cardiac valvular abnormalities (mitral valve prolapse and aortic, mitral, tricuspid regurgitation)
- Pericardial effusion
- Other cardiac abnormalities: congenital heart malformations, primary cardiomyopathies (eg, dilated, hypertrophic, and left ventricular noncompaction), atrial fibrillation
- Thoracic aortic and cervicocephalic arterial dissection, coronary aneurysm
- Association with abdominal aneurysm is not firmly established but may be associated with uncontrolled HTN.

Pain (back, abdomen, head, chest, legs): Back pain may be due to compression of enlarged kidneys, ruptured or infected cyst, stones, malignancy.

Cyst infections

- Common pathogens: *E. coli, Klebsiella*, *Proteus*, *Enterobacteriaceae*
- Antibiotics: fluoroquinolones or trimethoprim-sulfamethoxazole for better cystic penetration for 4 to 8 weeks, up to 3 months; vancomycin or erythromycin if streptococcal or staphylococcal infection, metronidazole, or clindamycin if anaerobic organisms
- Drainage or surgical intervention may be necessary in case of poor response.
- Imaging: CT or MRI are generally adequate. Indium-labeled white blood cell scan or 18-fluorodexoyglucose-positron emission tomography may be considered to identify infected cyst.

Renal cell carcinoma (RCC): The incidence of clinically significant RCC in patients with ESKD from ADPKD is not increased compared to that of patients with ESKD from other kidney diseases.

Polycystic liver disease

- Occurs in more than 85% of patients by age 25 to 34 and 94% by age 35 to 46 (CRISP)
- Liver function is often preserved but can be complicated with transaminitis, cyst infections, and hepatic venous outflow obstruction (Budd Chiari).
- Enterobacteriaceae is the most common organism isolated in infected liver cysts.
- Progressive disease may be seen with pregnancies, oral contraceptives, and hormonal replacement therapy.

Cerebral aneurysms (most often in the anterior circulation of circle of Willis)

- Asymptomatic cerebral aneurysms may be detected in 5% of patients without a family history and up to 20% in those with a family history.
- High risk of rupture for aneurysms greater than 10 mm in diameter
- Screening indications: family history of aneurysms, personal history of aneurysms, high-risk occupations (eg, pilots), kidney transplantation, pregnancy, elective surgery. Screening recommendations apply to those with good life expectancy.
  - Small unruptured aneurysms require regular follow-up at 6 to 24 months.
  - Patients with family history and negative screening should be rescreened in 5 to 10 years.
  - Screening study of choice is time-of-flight MRI without gadolinium. Computed tomogram angiography may be performed if MRI is contraindicated.

Other complications

- Cysts in other organs: pancreas, prostate, epididymis. Ovarian cyst is not associated with ADPKD.
- Asymptomatic bronchiectasis, inguinal/abdominal hernia, colonic diverticulosis in patients with ESKD (increased risk of perforation in kidney transplant recipients), duodenal diverticula, seminal vesical cysts with defective sperm motility (although infertility is rare)

Management

Dietary

- Moderate dietary sodium restriction of less than 2.3 g/d (<100 mmol of sodium/d): Increased urine sodium correlates with increased TKV over time.
- Caffeine intake: Caffeine is a methylxanthine that increases intracellular cAMP levels in cultured renal epithelial cells which could potentially accelerate cystic growth. However, clinical studies failed to show increased cystic growth or GFR decline with caffeine intake.
- Adequate free water intake to minimize ADH secretion: However, high water intake has not been shown to reduce copeptin level or cystic growth.

- Maintain normal body mass index (BMI); moderate caloric restriction
- Cholesterol: LDL of less than 100 mg/dL, high-density lipoprotein (HDL) of greater than 50 mg/dL; low threshold for statins

HTN control

- Maintain a BP goal of 110/75 mm Hg or less in individuals aged 18 to 50 years with an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2. Otherwise, follow same HTN guidelines set for CKD from other causes.
- Renin-angiotensin inhibitors (HALT-PKD [Hypertension and Angiotensin-Converting Enzyme Inhibition to Lower Progression of Polycystic Kidney Disease] trial):
  - ACEi (angiotensin-converting enzyme inhibitor) alone adequately controlled HTN in most patients. The addition of angiotensin receptor blocker (ARB) did not provide any additional benefits.
  - Lowering BP below goal (target 95-110/60-75 mm Hg) in young patients with good kidney function reduced rate of TKV increase by 14%, renal vascular resistance, urine albumin excretion, and left ventricular mass. The rate of decline in eGFR, however, was not significantly different.
- Diuretics in ADPKD:
  - Patients with ADPKD may have higher aldosterone levels and salt retention compared to those without the disease. Diuretic use may thus be beneficial.
  - DIPAK trial (Developing Interventions to Halt Progression of ADPKD 1) revealed that thiazide use was not associated with acceleration of renal function decline. Of note, however, 89% of thiazide users also used RAAS inhibitors.
- Calcium channel blockers (CCB) in ADPKD:
  - There are concerns that CCB may accelerate cystic growth. CCB has been shown to worsen ADPKD progression in rats.
  - Clinical studies have also revealed worse kidney function outcome among patients with ADPKD who received CCB:
    - A small retrospective study from Japan revealed worse kidney function among those receiving CCB compared to those receiving RAAS inhibition over an average follow-up of 2.4 years.
    - Post hoc analysis of the DIPAK-1 trial also revealed worse eGFR outcome among CCB users compared to those not receiving CCB.
    - CCB should be reserved as third-line antihypertensive therapy.
- Data for safety and efficacy for other antihypertensive classes are lacking.

ESKD/kidney replacement therapy

- Five-year survival of patients with ADPKD undergoing hemodialysis (HD) is superior to those with other kidney diseases.
- Compared with arteriovenous grafts and fistulas, the use of catheters for HD in ADPKD is associated with an increased risk for renal and liver cyst infections.
- Peritoneal dialysis (PD) is not contraindicated. However, there is a higher risk of abdominal wall hernia. Overall survival and peritonitis rates are similar to those in

nondiabetic PD patients.

- Patients with ADPKD have been reported to have higher hemoglobin levels and lower requirement for erythropoiesis-stimulating agents. This effect is thought to confer survival benefits among patients with ADPKD over those with other kidney diseases.

Kidney transplantation

- There is no difference in patient or graft survival among patients with ESKD due to ADPKD compared to those with other kidney diseases.
- Kidney volumes have been shown to decrease by 40% whereas liver volumes increase by 20% at 3 years posttransplantation.
- Deceased ADPKD kidneys with good function and relatively small size may still be considered for recipients who consent.
- Notable posttransplant complications: new-onset diabetes, GI complications (eg, perforation from diverticulosis), erythrocytosis, urinary tract infections, thromboembolic complications, hemorrhagic strokes

Direct medical therapies of ADPKD

ADH receptor antagonists, aka AVR2 (vasopressin receptor 2) antagonists (tolvaptan)

- Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes 3:4 Trial (TEMPO 3:4): Tolvaptan reduced kidney growth by 45% and eGFR decline by 26% over 3 years in "early" ADPKD. "Early" was defined as having creatinine clearance of greater than 60 mL/min.
- Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE trial): eGFR decline reduced by 35% in advanced ADPKD over 1 year. "Advanced ADPKD" was defined as having eGFR 25 to 65 mL/min/1.73 m^2.

Tolvaptan was approved for use in adult patients with ADPKD by the U.S. Food and Drug Administration (FDA) in 2018.

- Patients who most likely benefit from tolvaptan may be identified as having all of the following:
  - High risk of disease progression, identified as having ADPKD Mayo Class 1C, 1D, or 1E. The ADPKD Mayo Classification is based on kidney volume measurements (from CT without contrast or MRI without gadolinium), age, gender, race, height, and GFR.

FYI

The Mayo classification calculator may be found on their website (Classification of Typical ADPKD Calculator). The frequency of ESKD at 10 years increases from subclass 1A to 1E. In the younger CRISP cohort (age 15-46 years), the rate of ESKD at 10 years was 2.2% and 22.3% for those categorized as 1C and 1E, respectively. In the older Mayo cohort (age 15-80 years), the rate of ESKD at 10 years was 2.4% and 66.9% for patients categorized as 1A and 1E, respectively.

  - eGFR of 25 mL/min/1.73 m^2 or more
  - Age: 18 to 55 years old
- Due to concerns for liver toxicity, physicians prescribing tolvaptan must be trained in its use and patients receiving tolvaptan must be well informed of side effects and closely monitored. See Otsuka America Pharmaceutical, Inc. website for Jynarque (tolvaptan) for more information.
- Adverse effects: transaminitis, severe hepatocellular toxicity, polyuria, volume depletion, renal potassium wasting, thirst, hyperuricemia (rarely gout), drug interactions (Tolvaptan is a CYP3A4 substrate.)
- Patients with ADPKD Mayo Class 2 disease are only managed with conservative therapy. Mayo Class 2 refers to atypical presentations (eg, unilateral or segmental/asymmetric disease or bilateral disease with parenchymal atrophy).

Alternate criteria to identify patients at high risk for progression and consideration for tolvaptan when TKV cannot be calculated:

- Adults aged 55 years or below with eGFR less than 65 mL/min/1.73 m^2
- Average kidney length (by ultrasound, MRI, or CT) greater than 16.5 cm
- PROPKD (Progression of Polycystic Kidney Disease) score of greater than 6 in patients who have genetic data

FYI

Calculation of PROPKD score is based on:

- Gender (male = 1 point)
- Onset of HTN before 35 years of age (2 points)
- First urologic event before 35 years of age, defined as having gross hematuria, cyst infections, and flank pain related to cysts (2 points)
- PKD2 mutation (0 point)
- Truncating PKD1 (4 points)
- Nontruncating PKD1 mutation (2 points).
- The PROPKD score ranges from 0 to 9, where 0 to 3 points are considered low risk; 4 to 6 points, intermediate risk; and 7 to 9 points, high risk for progression to ESKD, with corresponding median ages for ESKD onset of 70.6, 56.9, and 49 years.
- Limitations to PROPKD score
  - Genetic testing is required.
  - PROPKD score can misdiagnose rapid progression in patients aged below 35 years unless they are already hypertensive and have experienced urologic complications.
  - PROPKD provides accurate prognosis for patients with ADPKD on a subpopulation level, but precision has not been determined on an individual level.

See **Appendix A6.4** for other potentially beneficial medical therapies still lacking robust supporting data.

Indications for nephrectomy

- Debilitating symptoms or intractable pain due to massively enlarged kidneys
- Life-threatening cystic hemorrhage not controlled by conservative management, intra-arterial embolization

- Cystic or recurrent infections not controlled by antibiotics and percutaneous drainage
- Evidence of RCC

Management of ADPKD-associated complications

Pain

- Pain management based on the sequential approach outlined by the World Health Organization's pain relief ladder is recommended.
- Others: celiac plexus blockade, radiofrequency ablation, spinal cord stimulation, laparoscopic or percutaneous transluminal catheter-based denervation

Gross hematuria

- Observation, hospitalization if severe, fluid support as needed
- Prolonged hematuria (ie, >7 days) dictates further evaluation for neoplasm.

Stones

- Maintain urine volume of greater than 2.5 L/d, dietary sodium restriction
- Supplement potassium citrate as needed for hypocitraturia and as tolerated per serum potassium level

Polycystic liver disease

- For severe polycystic liver disease, aspiration, sclerotherapy, fenestration, partial or segmental liver resection, or liver transplantation may be considered.
- Somatostatin analogs use is restricted to clinical trials or compassionate use.
- Cyst infections are best treated with percutaneous drainage and prolonged therapy with fluoroquinolones.

Pregnancy

- Increased risk for progression of liver cysts
- Increased risk for pregnancy-induced HTN and preeclampsia
- Multiple pregnancies (>3) are associated with a greater risk for GFR decline.

Tumor Syndromes With Cystic Kidneys

Tumor syndromes associated with cystic kidneys include:

- Tuberous sclerosis complex (TSC)
- von Hippel-Lindau (VHL) syndrome
- Birt-Hogg-Dube (BHD) syndrome
- All the three preceding conditions are associated with increased risk of RCC.

NOTE

The occurrence of bilateral RCC or RCC in young individuals should prompt consideration and evaluation for hereditary tumor syndromes. Unlike hereditary tumor syndromes, RCC in the general population is typically unilateral and focal and diagnosed later in life, that is, sixth to eighth decade of life.

Common pathogenesis of TSC, VHL, and BHD involves the inheritance of one copy of the mutated autosomal dominant gene (aka germline mutation) followed by somatic mutation of the normal gene copy later in life.

- Germline mutation associated with hereditary tumor syndromes:
  - TSC: TSC complex subunit 1 (TSC1) or subunit 2 (TSC2) tumor suppressor genes, encoding hamartin and tuberin, respectively
  - VHL: VHL, encoding VHL protein
  - BHD: FLCN, encoding folliculin
- Somatic mutation of the normal gene copy that occurs later in life gives rise to the full phenotypic presentation associated with the inherited germline mutation.

Tuberous sclerosis complex

Background:

- TSC is an autosomal dominant or sporadic disorder caused by pathogenic variants in either TSC1 or TSC2 or both.
- TSC occurs in 1 of 6,000 to 1 of 10,000 live births worldwide.
- Sporadic mutations occur in approximately 70% of cases.

Pathogenesis

- In normal cell growth, hamartin (TSC1) and tuberin (TSC2) form a hamartin-tuberin complex which exerts an inhibitory effect on mTOR, thereby effectively serving as a regulator of cell growth. Loss of function of the hamartin-tuberin complex results in dysregulated cell growth and formation of hamartomas, cystic disease, and RCC.
- TSC2-linked disease is typically (but not always) more severe (eg, more severe neurologic phenotype and higher risk for RCC) compared with TSC1.
- In sporadic (de novo) TSC cases, TSC2 mutations are 5 times more common than TSC1. Familial TSC cases involve TSC1 and TSC2 equally.
- Next generation genetic analysis can identify the pathogenic gene variant in more than 90% of cases.
- Of interest, PC1 also interacts with tuberin TSC1 and mTOR to regulate cell growth. The loss of PC1 function leads to the loss of regulated cell growth, hence cystogenesis in ADPKD1 (see **Figure 6.13**).

Clinical manifestations

- Classic Vogt triad (<30% of TSC): seizures, developmental delay, facial angiofibromas
- Renal involvement includes formation of cysts, angiomyolipoma (AML), glomerulocystic kidney disease (GCKD), clear-cell RCC, and FSGS with interstitial fibrosis.
  - Renal AML (**Figure 6.15**)

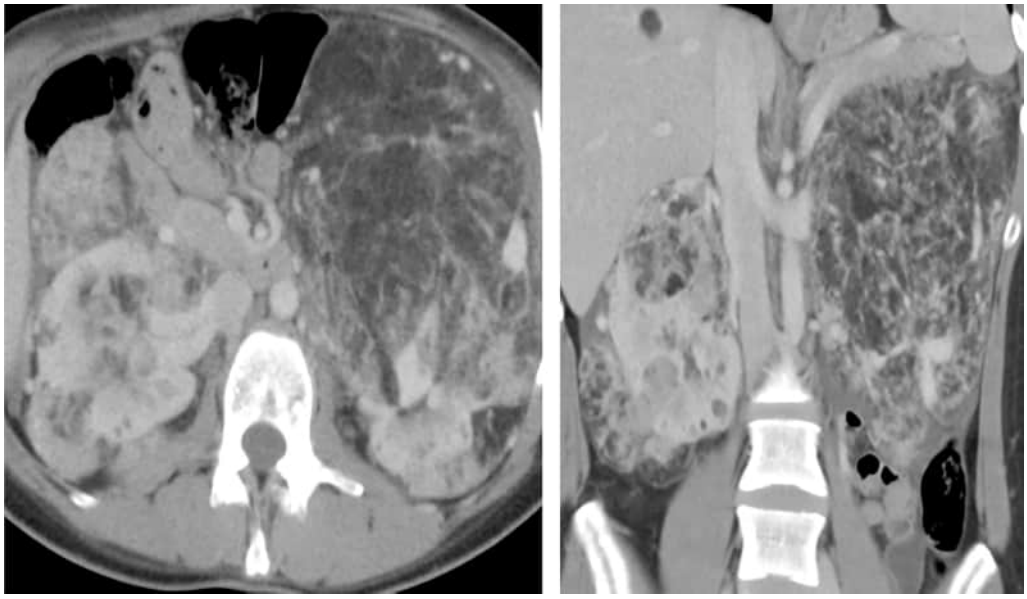


FIGURE 6.15 Renal angiomyolipoma. Axial and coronal postcontrast computed tomography images show very large angiomyolipoma (AML) in both kidneys in a patient with known tuberous sclerosis complex. The left renal AML is very large and at risk for bleeding. Note a small AML in the liver.

    - AML may occur in 60% to 70% of cases. Typically, there are bilateral and multiple lesions (vs single lesions in the general population).
    - AML may be more severe in women.
    - There is an increased risk of rupture during pregnancy and length of greater than 4 cm.
  - Renal cysts manifest in 20% to 30% of cases and may derive from any nephron segment. The presence of both AML and renal cysts is highly suggestive of TSC.
  - TSC-associated RCC may occur in 2% to 4% of cases. RCC are often bilateral and multifocal but tend to be more slowly progressive than those in the general population.
- Lymphangioleiomyomatosis (LAM) occurs almost exclusively in women.
- Others:
  - Brain: subependymal giant-cell astrocytomas (SEGA) and other central nervous system (CNS) tumors, intellectual disability, seizures, autism
  - Lungs: pulmonary LAM ± spontaneous pneumothorax
  - Cardiac: cardiac rhabdomyomas
  - Skin: angiofibromas, periungual fibromas, hypomelanotic macules (ash leaf spots, Shagreen patches)
- Patients with TSC are at risk for malignant tumors involving organs such as kidneys, brain, and soft tissues.

Diagnosis

- Genetic testing: The presence of either a TSC1 or TSC2 pathogenic variant from a nonlesional tissue is sufficient to diagnose TSC, regardless of clinical findings.
- Clinical criteria for "definite diagnosis": two or more major features, or one major with two or more minor features
  - Major features: hypomelanotic macules, angiofibromas, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cerebral cortical glioneural hamartomas, subependymal nodules, SEGA, cardiac rhabdomyoma, LAM*, AML*
  - Minor features: "confetti" skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patch, multiple renal cysts, nonrenal hamartomas

NOTE

*A combination of LAM and AML without other features does not meet diagnostic criteria for TSC. Some females present with both but without other TSC manifestations or increased risk of having an affected child.

Management

- mTOR inhibitors: Everolimus may be used as adjunctive therapy for TSC-associated partial onset seizures and treatment of symptomatic SEGA not curable by surgery. Everolimus and sirolimus may be beneficial in treating systemic TSC manifestations including facial angiofibromas, AML, and pulmonary LAM.
- Renal AML
  - Prophylactic surgery or vascular coiling/thrombosis may be considered if greater than 4 cm
  - Advise women with AML of potential accelerated AML growth and hemorrhagic complications with estrogen replacement therapy.
- RCC
  - Surgical decompression of large symptomatic cysts refractory to medical therapy
  - Nephron-sparing surgical resection of renal carcinoma is generally suggested due to the tendency for bilateral renal involvement.
  - Bilateral nephrectomies are recommended at ESKD (dialysis or transplant).
- Surveillance: Obtain abdominal CT or MRI every 1 to 3 years lifelong to assess AML and cystic progression as well as malignancy transformation. Frequency of imaging study depends on size and growth rate of lesions.

TSC/PKD1 contiguous gene syndrome

- TSC/PKD1 contiguous gene syndrome is caused by a deletion mutation involving both TSC2 and PKD1 genes that result in severe PKD with TSC features.
- Occurs in 2% to 3% of patients with TSC
- Age of onset: first year of life; ESKD by the age of 20
- Ultrasound: large kidneys similar to ADPKD

VHL disease

- VHL disease is an autosomal dominant disorder caused by a germline mutation of one VHL gene copy and a somatic mutation of the second copy later in life, resulting in multiorgan predisposition to benign and malignant tumors.
- Autosomal mutation occurs in 80% of cases and sporadic in 20%.
- Occurs in 1 out of 36,000 live births and affects all ethnicities

Pathogenesis

Autosomal dominant mutation of VHL gene encoding the VHL protein. VHL protein is part of the ubiquitin-ligase complex involved in ubiquitination and subsequent degradation of the α subunit of the hypoxia-inducible factor HIF-1 and HIF-2. Accumulated HIF-α binds to HIF-β, translocates to nucleus, binds to the hypoxia response element to induce transcriptions of vascular endothelial growth factor (VEGF), erythropoietin, tumor growth factor-β1, platelet-derived growth factor, among others (see **Figure 4.1**).

Clinical manifestations of VHL disease

- Onset of disease is typically between second and third decade of life, with more than 90% occurs by age 65.
- Associated tumors: retinal or CNS hemangioblastomas, clear-cell RCC, pheochromocytomas, serous cystadenomas and neuroendocrine pancreatic neoplasms (but not pancreatic adenocarcinomas), endolymphatic sac tumors (potential hearing loss if bilateral disease), renal and pancreatic cysts, epididymal or broad ligament cystadenomas
- VHL-associated RCCs
  - Lifetime risk of approximately 70%
  - Tend to be clear-cell RCC and slower growing than those seen in sporadic cases

Diagnosis

- Presence of one tumor (retinal or cerebellar hemangioblastoma, RCC, or pheochromocytoma) if positive family history, two tumors if no family history, or genetic testing
- Renal imaging: normal kidney size with cysts in more than 50% of cases. Cysts typically present in small number and small size. While not all renal tumors are preceded by cysts, all renal cysts must be considered preneoplastic and closely monitored.
- Obtain plasma free metanephrines to evaluate for pheochromocytomas.

Management

- Annual BP checks, pheochromocytoma screen, MRI or CT of kidneys and CNS
- RCC:
  - Surveillance for asymptomatic RCC of less than 3 cm with slow growth rate may be appropriate due to low metastatic potential. The use of belzutifan, a HIF-2α inhibitor, may be considered in those with accelerated tumor growth, that is, greater than 5 mm/y. Hypoxia and anemia are potential complications associated with belzutifan and must be monitored and managed closely. Of note, belzutifan

may also be considered in the treatment of VHL-associated CNS hemangioblastomas and pancreatic neuroendocrine tumors.

  - Renal-sparing surgery is appropriate for RCC of 3 cm or more in size due to multifocal nature of RCC. Radioablative therapy or other ablative techniques may be considered for multicentric lesions.
- Medical therapies with promising results include multiple tyrosine kinase inhibitors (eg, sunitinib, pazopanib), anti-VEGF-antibody (eg, bevacizumab), mTOR inhibitor (eg, everolimus), and checkpoint inhibitors (eg, anti-PD-1 [nivolumab], inhibitor of CTLA-4 [ipilimumab]).

BHD syndrome

- Autosomal dominant mutation of the tumor suppression folliculin gene FLCN. Folliculin is involved in cell-cell adhesion, cell polarity, mTOR signaling pathways, and ciliogenesis. Loss of folliculin function can lead to dysregulated cell growth and tumor formation.
- Heterozygous inheritance of the mutated FLCN gene is enough to cause fibrofolliculomas and pulmonary cysts but not enough to cause RCC. Random mutation of the normal FLCN copy later in life is required for dysregulated cell proliferation in the kidneys and RCC.
- Clinical manifestations: RCC (30%), fibrofolliculomas (white papular lesions on nose and cheeks), cystic lung disease, recurrent spontaneous pneumothorax
- Diagnosis may be made by genetic testing.
- Management: Detect and treat renal tumors and pulmonary complications.

Other Cystic Diseases

Autosomal recessive polycystic kidney disease (ARPKD)

- ARPKD is an inherited disease caused by mutations of the polycystic kidney and hepatic disease 1 (PKHD1) gene encoding fibrocystin/polyductin (FCP).
- Mutations of FCP lead to abnormal fusiform or saccular dilation of the collecting ducts and abnormal remodeling of the biliary system, resulting in renal cystic disease and progressive portal fibrosis, respectively.
- Patients may present with combined severe kidney and liver disease, mild disease of one organ and severe disease of the other, mild disease of both organs, or isolated hepatic fibrosis and nonobstructive dilation of intrahepatic bile ducts (Caroli disease).
- ARPKD occurs in 1 of 20,000 live births; carrier rate: 1 in 70

Pathogenesis

FCP is a transmembrane protein found in mitotic spindle, microtubules, and apical primary cilia in biliary and renal tubular epithelia. FCP interacts with PC2 in renal tubules and biliary ducts and is thought to play a central role in microtubule formation and function and epithelial proliferation and secretion.

Clinical manifestations

- The majority of patients present in utero or at birth.
- In utero presentation includes enlarged echogenic kidneys, poor kidney function, and oligohydramnios. The latter may lead to abnormal fetal development, Potter phenotype consisting of pulmonary hypoplasia, characteristic facies, and spine and limb deformities.
- Perinatal mortality is estimated to be 25% to 30%.
- Children may present with urinary concentrating defect and volume depletion.
- ESKD is reached in more than 60% by age 10.
- Hepatobiliary complications: hepatosplenomegaly, portal HTN, hepatic fibrosis, ascending cholangitis, cholangiocarcinoma

Imaging studies

- Ultrasound:
  - Enlarged kidneys with poor corticomedullary differentiation due to the hyperechoic medulla, peaking in first 1 to 2 years of age, then reduce in size in subsequent years
  - Radially arrayed dilated collecting ducts spanning from cortex to medulla may be seen with high resolution ultrasound.
  - ARPKD cysts are not discrete sacs as those seen in ADPKD, TSC, and VHL disease.
- CT:
  - Nephromegaly with renal attenuation values similar to water due to dilated collecting ducts
  - Striated nephrogram due to the stasis of contrast medium in dilated tubules
  - Pelvicaliectasis and renal calcifications

Diagnosis

- Histopathology: elongated cystic dilatation of the collecting ducts in a linear pattern perpendicular to the capsule extending from medulla to cortex. See **Figure 6.16**.
- Genetic testing

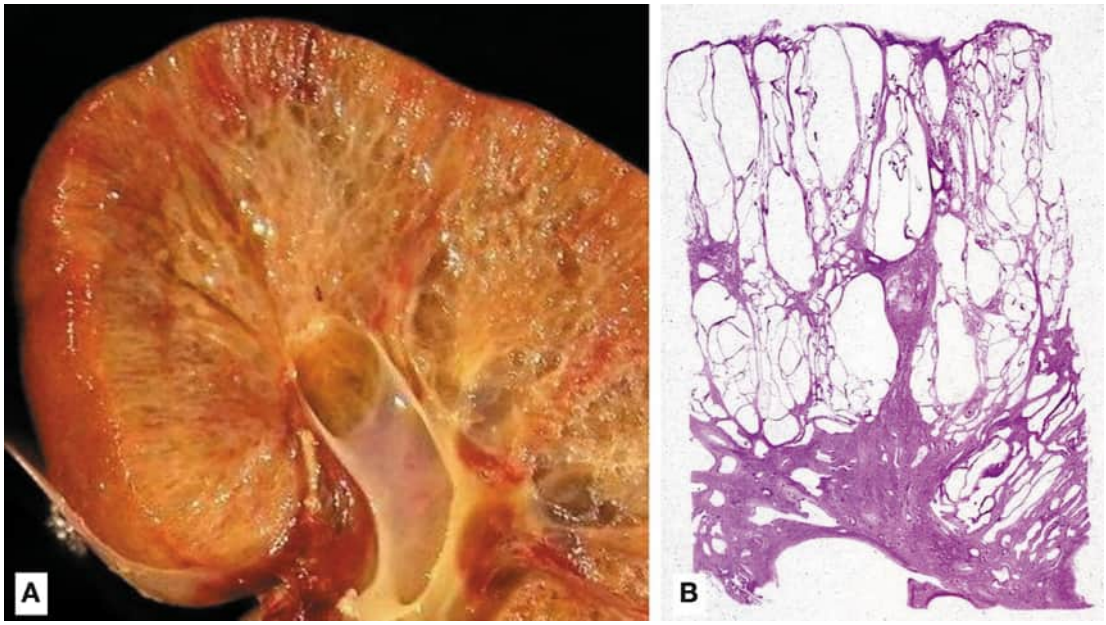


FIGURE 6.16 **Autosomal recessive polycystic kidney disease.** A. Kidney with cystic dilatation of the collecting ducts in a linear pattern perpendicular to the capsule. B. Collecting duct cysts extending from the medulla to the cortex with a linear arrangement (hematoxylin and eosin).

Management

- BP control with RAAS inhibitors
- Thiazide diuretics may be considered for severe concentrating defect and polyuria.
- Maintain high index of suspicion for ascending cholangitis.
- Kidney transplantation is preferred in ESKD. Combined kidney and liver transplantation should be considered in cases with extensive portal HTN. Parental organ donation is possible if normal imaging studies of kidneys and liver due to the recessive nature of disease.

Medullary sponge kidney (MSK)

- MSK is a rare condition characterized by dilatation of terminal collecting ducts in the pericalyceal regions of renal papillae. Clinically, patients may present with nephrocalcinosis, recurrent calcium kidney stones, distal renal tubular acidosis, and hypocitraturia.
- The prevalence of MSK is estimated to be between 5/10,000 and 5/100,000 and thought to be higher among individuals with recurrent kidney stones.
- MSK is mostly sporadic but rarely may present with familial clustering as autosomal dominant inheritance with variable penetrance.

Pathogenesis

- MSK is thought to involve genes imperative for proper renal formation and distal nephron development of precalyceal and collecting ducts.
- MSK may occur in association with other developmental defects or tumors (eg, PKD, Wilms tumor, horseshoe kidney, CAKUT syndrome, Caroli syndrome, Beckwith-

Wiedemann syndrome, Rabson-Mendenhall syndrome)

Clinical manifestations

- MSK is generally asymptomatic and diagnosed from an incidental finding.
- MSK may be complicated by hematuria, flank pain, urinary tract infections, nephrolithiasis (calcium phosphate or calcium oxalate), tubular mineral "plugs."
- Affected patients may have urinary concentrating and acidification defects resulting in incomplete distal RTA, hypercalciuria and alkaline urine, and bone mineralization defect.
- MSK usually does not lead to ESKD. However, complications from recurrent stone associated obstructions or infections may lead to CKD and ESKD.
- Some patients may present with hyperparathyroidism.

Diagnosis (Figure 6.17)

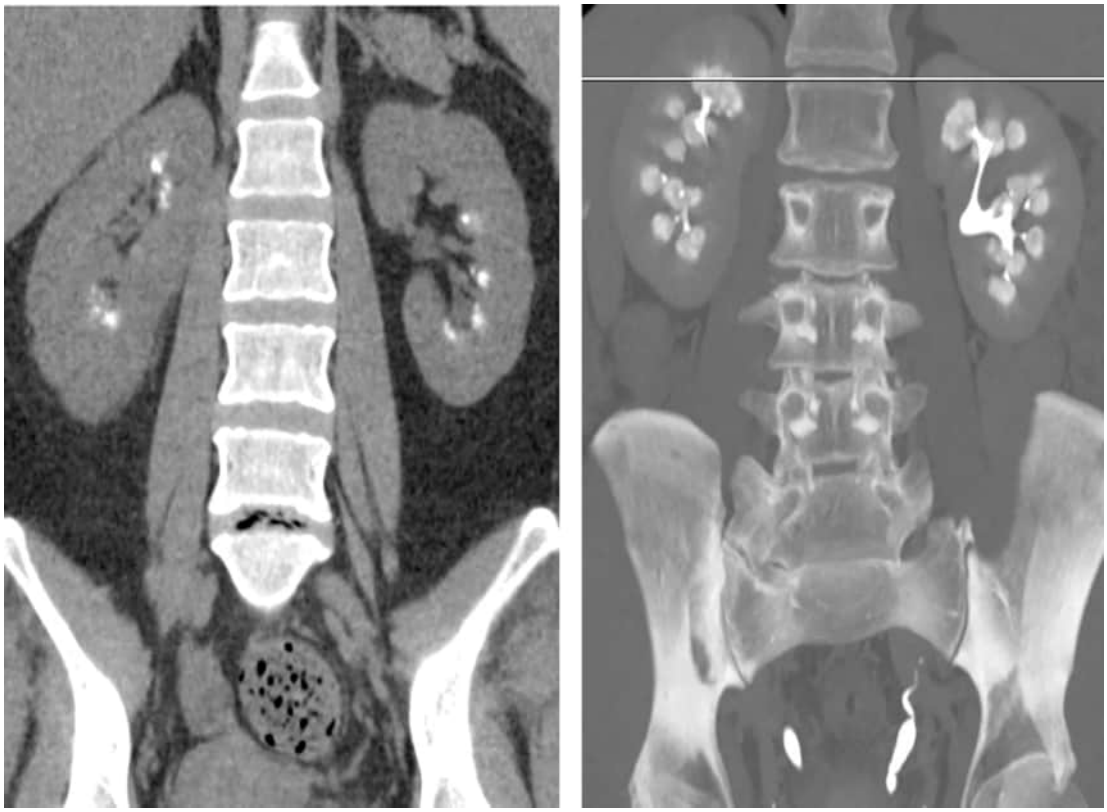


FIGURE 6.17 Medullary sponge kidney. Coronal noncontract computed tomography images showing amorphous and course pyramidal calcifications in both kidneys. Postcontrast excretory phase maximum intensity projection images show a "paintbrush" like appearance to the renal calyces.

- Abdominal radiographs revealing radiopaque concretions (calcium stones)
- Excretory urography revealing spherical cysts or diffuse linear striations due to contrast retention by dilated medullary and papillary collecting ducts. These findings may also be described as "bouquet of flowers" or "paintbrush."
- Nonenhanced CT may reveal echogenic, hyperdense foci in the medulla due to stones/nephrocalcinosis.

- Histopathology: bilateral multiple spherical or oval cysts (1-8 mm) in renal papillae that may communicate with the collecting system and contain calcium apatite concretions

Management

- Nephrolithiasis:
  - Potassium citrate and high fluid intake
  - Thiazides if recurrent stones
  - Inorganic phosphate if the first two options fail or are not possible. Avoid phosphates in patients with struvite stones. Recall struvite stones are "triphosphates."
  - Urologic interventions may be necessary if there are obstructing stones.
- Urinary tract infections:
  - Antibiotic selection per sensitivity
  - Aggressive and prolonged therapy are generally recommended.

Simple cysts

- Simple cysts are typically asymptomatic, solitary, and unilateral located in the renal cortex. Multiple and bilateral cysts may be seen.
- Simple cysts typically present in individuals over 50 years of age with a male predominance.

Pathogenesis: thought to be related to an initial ischemic event that leads to an aberrant hypertrophic response with subsequent cystic growth

Clinical manifestations

- Generally asymptomatic but may be associated with HTN (presumably due to renin produced from epithelial cells lining cysts) and erythrocytosis
- Cysts may rarely become infected with development of thickened walls and calcifications.

Management:

- Simple cysts are benign and generally do not require follow-up.
- Large cysts associated with severe HTN may be considered for drainage.
- Kidney transplantation: Growth rate of simple cysts does not increase with kidney donation in either the donor or recipient. Simple cysts do not adversely affect renal outcomes.

Acquired cystic kidney disease (ACKD)

Histopathology: small to large cystically dilated tubules in all parts of the nephron (glomeruli to collecting ducts) with epithelial cell hypertrophy and hyperplasia, including papillary projections of epithelium into cystic tubules (**Figure 6.18**)

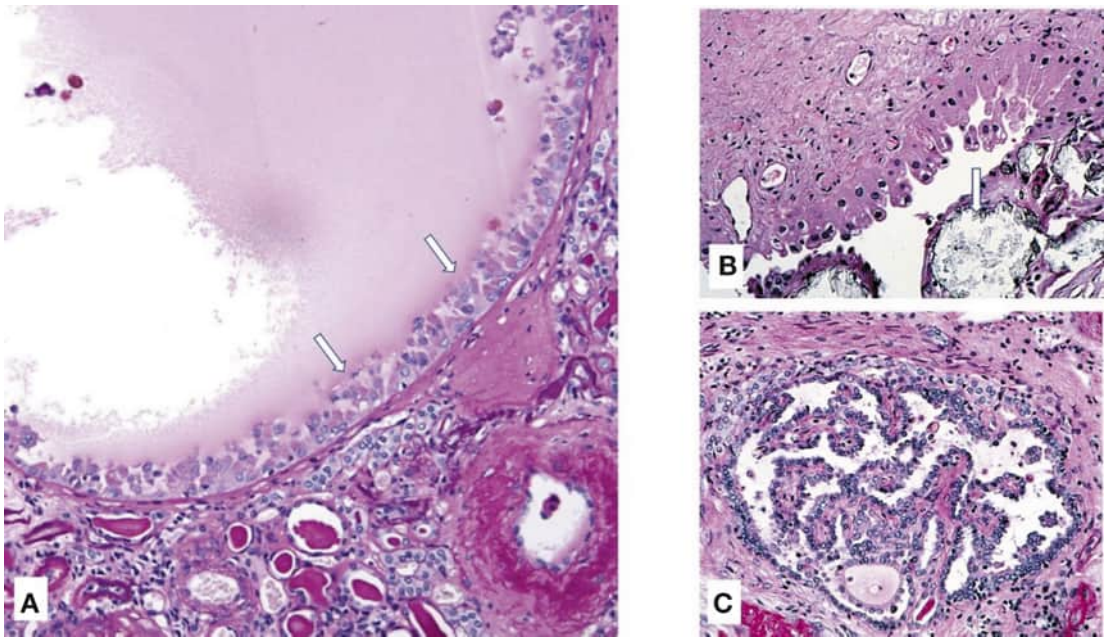


FIGURE 6.18 Acquired cystic kidney disease. A. Cystically dilated tubule with epithelial cell hypertrophy and hyperplasia (arrows) (periodic acid-Schiff). B. Cystically dilated tubule with epithelial cell hypertrophy and oxalate crystals (arrow) in the tubular wall (hematoxylin and eosin). C. Intratubular small papillary tubular cell adenoma (neoplasm). These are commonly found in the setting of acquired cystic disease (periodic acid-Schiff).

Conditions associated with ACKD:

- Chronic hypokalemia:
  - Cysts typically localize to renal medulla.
  - Resolution of cysts is possible after correction of hypokalemia (eg, adrenalectomy for functioning tumors).
- CKD-associated ACKD:
  - The incidence of ACKD increases with ESKD and dialysis vintage and may range from 50% to 80% among patients who receive HD or PD for 10 years or more.
  - Pathogenesis: similar to simple cyst plus presumed contribution from uremic milieu
  - Diagnosis: The presence of three or more cysts in each kidney of small to normal size
  - Risk: CKD and dialysis vintage
  - Clinical manifestations:
    - Cysts are typically less than 0.5 cm but may be up to 2 to 3 cm, generally asymptomatic.
    - ACKD is associated with an increased risk of adenomas and RCCs. Unlike sporadic clear-cell RCC, ACKD-associated RCC are typically multifocal and bilateral with lower proliferative activity and metastatic disease.

Screening and surveillance

- Screening in patients with pre-ESKD CKD is controversial and not well established.
- Dialysis patients: Annual screening has been suggested for patients who have received dialysis for 3 or more years and have a good life expectancy. Ultrasound is an acceptable screening study.
- Kidney transplant recipients: annual ultrasound screening of native kidneys
  - Bosniak I & II: ultrasound screening twice yearly or CT scan to evaluate for progression
  - Bosniak IIf: ultrasound evaluation 4 times a year; CT or MRI scan yearly; nephrectomy if progressive lesions, even if not reaching category III/IV
  - Bosniak III & IV: nephrectomy

NOTE

Bosniak CT-based cyst classification

Class I:

- Cyst with hairline thin wall; no septation, calcification, or solid component; no enhancement with contrast CT
- Management: benign cyst, no follow-up required

Class II

- Type 1:
  - Cyst with a few hairline thin septations; fine calcification or short segment of slightly thickened calcifications may be seen in cyst wall or septae.
  - Management: benign simple cyst, no follow-up required
- Type 2:
  - Uniformly high attenuation lesion of less than 3 cm, well-marginated, nonenhancing
  - Management: likely benign renal lesion, no follow-up required

Class IIF (F is for follow-up)

- Type 1: Cysts with multiple hairline thin septa or minimally smooth thickening of wall or septa ± subjective perceived enhancement (without measurable enhancement) with radiocontrast that may have thick or nodular calcifications.
- Type 2: Intrarenal nonenhancing hyperattenuating renal lesions of greater than 3 cm
- Management of IIF
  - Most Bosniak IIF masses are benign. When malignant, most are indolent. Follow-up at 6 and 12 months, then annually for 5 years to assess for changes
  - For kidney transplant recipients: ultrasound evaluation 4 times a year; CT or MRI scan yearly; nephrectomy if progressive lesions, even if not reaching category III/IV

Class III

- Cystic masses with thickened irregular or smooth wall/septa with measurable enhancement (Contrast enhancement implies vascularized mass, thus possible malignancy.)
- Management: Bosniak III masses have an intermediate probability of being malignant (cystic RCC and multiloculated cystic RCC). Other differential diagnoses include hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma. Consult urology.

Class IV

- All components of Class III plus the presence of soft tissue components/nodules with measurable enhancement adjacent to and independent of cyst wall or septum
- Management: A large majority of Bosniak IV cystic renal masses are malignant. Consult urology.

For interested readers, a proposed detailed update of current Bosniak classification is reviewed in Silverman et al., Bosniak Classification of Cystic Renal Masses, Version 2019.

Multilocular cystic nephroma, aka papillary cystadenoma, benign cystic nephroma

Multilocular cystic nephroma is a benign mixed mesenchymal and epithelial slow-growing neoplasm in the kidney (**Figure 6.19**).

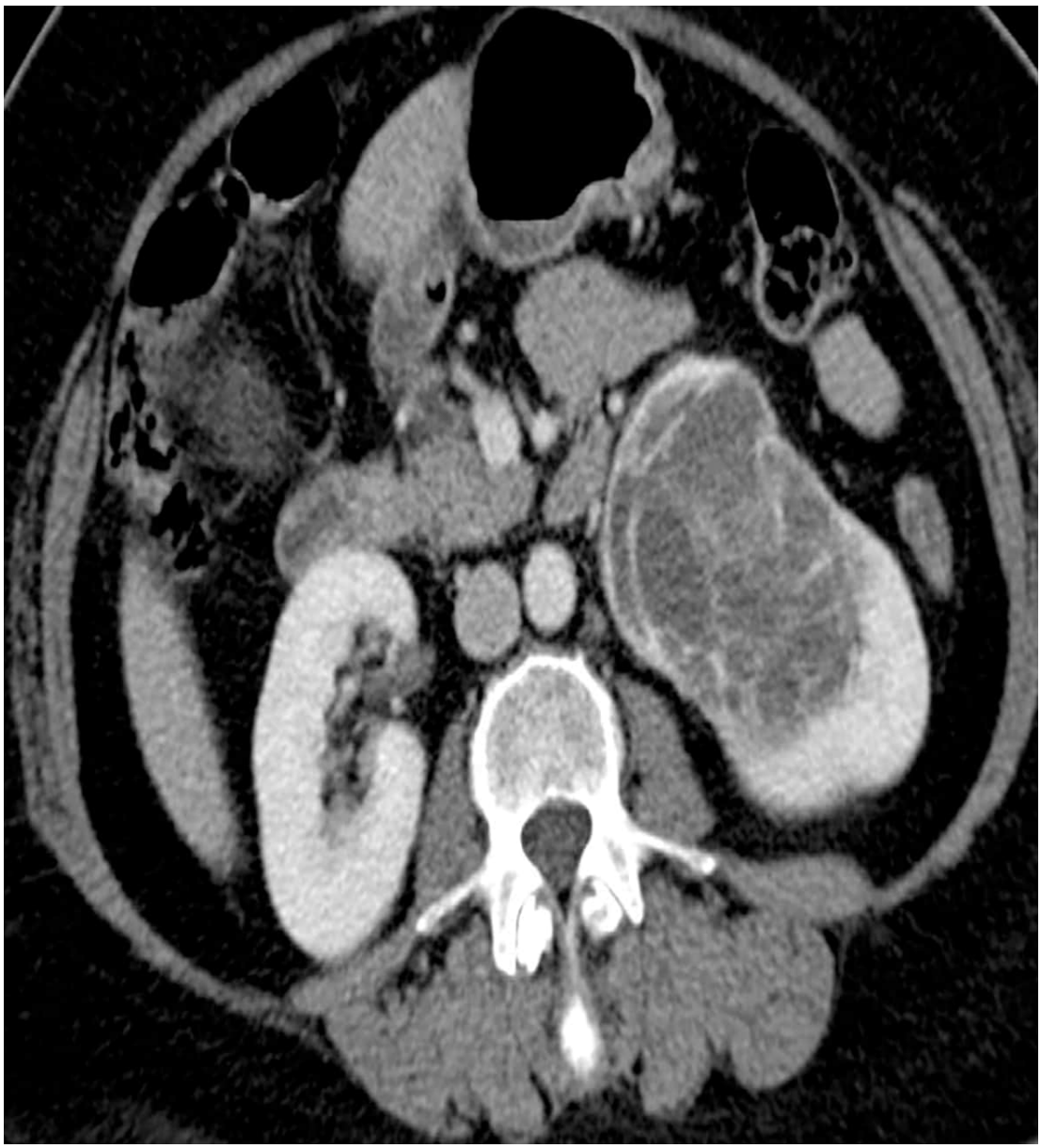


FIGURE 6.19 **Multilocular cystic nephroma.** Axial postcontrast computed tomography image showing a well-circumscribed multilocular cystic mass with septal enhancement. This lesion is indistinguishable from renal cell carcinoma on imaging.

Diagnosis

- Ultrasound findings:
  - Unilateral mass with irregular cysts and septa of variable thicknesses
  - Generally classified as Bosniak III that require surgery to exclude malignancy

- CT findings:
  - Well-circumscribed cystic mass with hypoattenuated components with no contrast excretion into cystic components
  - Contrast enhancement of septa may be seen.

Clinical manifestations

- Follows a bimodal age and sex pattern: boys 3 months to 4 years; postmenopausal women aged 40 to 60 years
- Abdominal/flank pain, palpable mass, hematuria, HTN
- Complications: calculi, urinary tract infections, carcinomatous degeneration

Management: surgical resection

Glomerulocystic kidney disease

- Histopathology: cystic dilation of Bowman space often with mildly retracted glomerular tufts; there may be some cystic dilatation of the adjacent S1 proximal tubules.
- GCKD can present as an isolated condition, infantile manifestation of ADPKD, part of a disease syndrome involving a heritable malformation syndrome (eg, TSC, VHL), acquired and dysplastic kidneys, or familial hypoplastic kidneys.
- Patients with familial hypoplastic GCKD present with relatively small kidneys with medullocalyceal abnormalities and variable associations with gynecologic abnormalities and maturity-onset diabetes of the young type 5 (MODY5).
- Ultrasound may be notable for increased echogenicity of renal cortex with minute cysts. Associated renal medullary dysplasia and biliary dysgenesis may be found in infants with familial or sporadic GCKD.

Table 6.3 summarizes major renal cystic diseases and important associated clinical features.

CHAPTER 7

Glomerular and Vascular Disorders

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GENERAL MANAGEMENT CONSIDERATIONS FOR GLOMERULAR/VASCULAR DISEASES (KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES [KDIGO] 2021)

Kidney Biopsy Considerations

Kidney biopsy indications

Kidney biopsy should be performed when results will change management and/or refine prognosis. **Table 7.1** outlines kidney biopsy indications for patients who present with proteinuria and/or glomerular hematuria per KDIGO 2021.

Table 7.1 Kidney biopsy indications (KDIGO 2021)

Need for kidney biopsy	Conditions
Perform kidney biopsy.	• Kidney biopsy is the gold standard for diagnosing glomerular diseases. • [a]A biopsy should be performed if the result is expected to guide treatment and/or better inform prognosis.
Treatment may be initiated without a kidney biopsy diagnosis.	• Anti-PLA2R antibody-positive membranous nephropathy (especially with normal eGFR) • Myeloperoxidase- or proteinase 3–positive ANCA vasculitis • [b]Anti-GBM disease • [c]Alport disease • [c]Fabry disease • Familial focal segmental glomerulosclerosis in families with well-characterized mutations • Systemic lupus erythematosus • Biopsy contraindicated per clinical judgment
Kidney biopsy may not needed.	• Children <12 y old • Steroid-sensitive nephrotic syndrome • Poststreptococcal glomerulonephritis

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; KDIGO, Kidney Disease: Improving Global Outcomes.

[a]A kidney biopsy may also be performed at the discretion of the nephrologist (eg, new unexplained active urinary sediment or worsening proteinuria).

[b]In the presence of positive anti-GBM antibodies and classic presentation.

[c]Positive genetic analysis or low α-galactosidase A activity in leukocytes of males with positive family history.

Adapted from Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int.* 2021;100(4S):S1-S126, with permission from Elsevier.

Kidney biopsy adequacy

- In general, a minimum of 8 to 10 glomeruli/biopsy
- Diffuse and global diseases may be diagnosed with one glomerulus (membranous nephropathy [MN], immunoglobulin A nephropathy [IgAN]). However, activity, chronicity, and other findings require more tissue.
- Focal segmental glomerulosclerosis (FSGS) may only be seen in a small portion of glomeruli, and of those affected, only segments of glomeruli. FSGS may require 20 or more glomeruli for increased diagnostic sensitivity.

Repeat kidney biopsy indications

- Initial biopsy is inadequate for diagnosis.
- Biopsy results will change management and/or refine prognosis.
  - Poor response to therapy
  - Unexpected deterioration of kidney function
  - Clinical or laboratory findings suggesting a change in the severity of same disease (eg, conversion of membranous to active diffuse lupus nephritis [LN])
  - Clinical or laboratory findings suggesting a new disease process
  - Unclear cause of glomerular filtration rate (GFR) deterioration (ie, chronic progression vs active disease)
  - Determination of disease chronicity for treatment decisions (ie, stop treatment due to advanced end-stage disease)
- Methods of analysis of kidney biopsy samples are outlined in **Table 7.2**.

Table 7.2 Kidney biopsy adequacy

Kidney biopsy adequacy depends on a composite of biopsy sample size and microscopic analyses.

Biopsy specimen size	

• Usually >8-10 glomeruli are needed to diagnose or exclude a specific histopathologic pattern with reasonable confidence.
• Exceptions:
  • [a]Even a portion of one glomerulus can diagnose diffuse and global disorders such as MN, IgAN but will not give activity and chronicity information.
  • >20 glomeruli often needed for a diagnosis of FSGS given the focal nature of the diagnostic lesion.	

Microscopic analysis	
Light microscopy (LM)	• Initial evaluation is based on morphologic pattern of appearance observed with periodic acid-Schiff, hematoxylin and eosin, Masson trichrome, and Jones methenamine silver stains.

Kidney biopsy adequacy depends on a composite of biopsy sample size and microscopic analyses.

Immunofluorescence (IF) microscopy	• Detects traditional immunoreactants • IgG, IgA, IgM, C3, C4 and/or C1q, fibrin, λ, κ light chains, ±albumin
Additional IF, immunohistochemistry (IHC)	• Detects target antigens • PLA2R, THSD7A, NELL1 (MN), DNAJB9 (fibrillary GN), fibronectin, lipoproteins, collagen III, collagen IV (a3, a5 chains), amyloid types (AL, AA, LECT2, ATTR)
Electron microscopy (EM)	Determines: • Deposit location, extent, and ultrastructural characteristics • Foot process effacement extent, GBM structural changes • Endothelial injury patterns

Abbreviations: AA, amyloid A; AL, amyloid light chain; ATTR, amyloid transthyretin; DNAJB9, DnaJ homolog subfamily B member 9; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; IgG, immunoglobulin G; LECT2, leukocyte chemotactic factor 2; MN, membranous nephropathy; NELL1, neural epidermal growth factor-like 1; PLA2R, phospholipase A2 receptor; THDS7A, thrombospondin domain-containing 7A.

[a]While a limited diagnosis can be made from a suboptimal kidney sample size, additional information (activity, chronicity, presence of secondary FSGS or crescents) will not be available.

Management of Complications Common to Glomerular/Vascular Diseases

Hypertension

Goal blood pressure (BP): target BP less than 120 mm Hg

Lifestyle modifications: salt restriction, weight optimization, exercise, smoking cessation

Clinical data support the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) as first-line therapy

- Educate patients regarding discontinuation of ACEi/ARB in volume-depleted states.
- Monitor serum creatinine (SCr) and K^+ frequently: Do not discontinue ACEi/ARB in patients with modest but stable SCr increase (up to 30%).
- K^+-lowering medications may be considered if hyperkalemia limits ACEi/ARB tolerability.

Mineralocorticoid receptor antagonist (eg, spironolactone, eplerenone)

- Useful antihypertensive and antiproteinuric agent, particularly in ACEi/ARB-intolerant patients
- May require discontinuation for hyperkalemia. Salvage therapy with K^+ binders may be feasible.

Additional strategies:

- Other antihypertensive agents that may also reduce proteinuria: nondihydropyridine calcium channel blocker (CCB) (eg, diltiazem, verapamil) > β-blockers, diuretics, α1-blockers
- Loop and thiazide diuretics improve BP control, reduce hyperkalemia, and enhance the antiproteinuric effect of inhibitors of the renin-angiotensin aldosterone system (RAASi).

- Dihydropyridine CCB, methyldopa, and guanfacine do not reduce and may increase proteinuria.

Proteinuria

Quantification of proteinuria

- 24-Hour urine protein collection
  - Always include urine creatinine to assess collection adequacy.
  - Ideal and preferred for patients with glomerulonephritis (GN) where initiation or intensification of immunosuppressive therapy (IST) is necessary
- Urine protein-to-creatinine ratio (uPCR) from an aliquot of an attempted 12- to 24-hour urine collection is the next best option.
- Random spot uPCR sampling is discouraged due to variations in both protein and creatinine associated with time of day and level of physical activity.
- First-morning urine collections may underestimate 24-hour urine protein excretion in orthostatic proteinuria.
- Proteinuria 3.5 g/24 h or more or uPCR 3 g/g or higher defines nephrotic range proteinuria.

Medical therapy for proteinuria

- ACEi or ARB may reduce proteinuria by 40% to 50%.
- Combination may result in additive antiproteinuric effect, but hyperkalemia and acute kidney injury (AKI) may also be additive and unacceptable. See hypertension (HTN) management above for other antihypertensive agents with antiproteinuric effects.

Hematuria

- Routine evaluation of urine sediment for erythrocyte morphology (dysmorphic and microcytic compared to peripheral red blood cells [RBCs]), RBC casts, and/or acanthocytes (>5% of all RBCs) is indicated in all forms of glomerular disease.
- Monitoring hematuria (presence of RBCs) may provide prognostic value in many forms of glomerular diseases, particularly IgAN and vasculitis.

Hyperlipidemia

- Statin use should be per standard guidelines for those with increased cardiovascular (CV) risks.
- Statins have not been proven to reduce cardiovascular events (CVEs) in nephrotic syndrome (NS) (particularly minimal change disease [MCD]).
- The renoprotective effect of statins in slowing GFR decline is not established.
- Nonstatin considerations for patients who cannot achieve low-density lipoprotein cholesterol (LDL-C) or triglyceride goals despite being on maximally tolerated statin dose or cannot tolerate statin:
  - Bile acid sequestrants, fibrates, nicotinic acid, ezetimibe, or proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor
  - Lipid apheresis

Nephrotic edema

- Dietary sodium restriction 1.5 to 2.0 g (60-90 mmol) daily
- Intravenous (IV) loop diuretics should be considered if anasarca is present because bowel wall edema limits oral medication absorption. Twice-daily administration is preferred.

Furosemide-resistant edema

- Consider longer acting loop diuretics such as torsemide or bumetanide.
- Add thiazide, thiazide-like diuretics, or acetazolamide to loop diuretic.
- Acetazolamide helps with loop diuretic–induced metabolic alkalosis.
- Potassium-sparing diuretics (eg, spironolactone or amiloride) are helpful for maintaining potassium balance and synergize with loop diuretics for diuresis.
- Consider albumin infusion with diuretics, although this is of unproven benefit for NS.

Hypercoagulability

- Increased thromboembolism (TE) risk in patients with NS with serum albumin less than 2.5 g/dL
- Full anticoagulation with heparin or warfarin (target international normalized ratio [INR] 2-3) for 6 to 12 months and/or for the duration of the NS is indicated in patients with known thromboembolic events associated with NS.
- Consider prophylactic full-dose anticoagulation if serum albumin less than 2.0 to 2.5 g/dL AND one or more of the following: proteinuria greater than 10 g/d, body mass index greater than 35 kg/m^2, family history of TE with documented genetic predisposition, the New York Heart Association (NYHA) functional class III or IV congestive heart failure, recent abdominal or orthopedic surgery, or prolonged immobilization. Risks of serious life-threatening bleeding complications must be weighed (see Prophylactic Anticoagulation in Patients with Membranous Nephropathy: A Decision Analysis on the University of North Carolina's School of Medicine website).
- During heparin anticoagulation, a higher than average dosing may be required because part of heparin action depends on antithrombin III, which may be lost with severe proteinuria.
- Aspirin may be used in lieu of heparin in patients with high bleeding risk.
- Neither the efficacy nor safety of direct thrombin and factor Xa inhibitors have been systematically studied in patients with NS.

Risk of infections

Vaccinations

- Pneumococcal, annual influenza, and recombinant herpes zoster (Shingrix) vaccines should be given. The effectiveness of the recombinant zoster vaccine may be diminished in patients taking corticosteroids. The live attenuated Zostavax vaccine is contraindicated with immunosuppression or immunodeficiency.
- Patients with household contacts should receive the influenza vaccine.

- Vaccination with both a meningococcal conjugate (MenACWY) and a serogroup B meningococcal (MenB) vaccine should be provided to patients receiving complement inhibitors (eg, eculizumab, ravulizumab, iptacopan). Since these may confer only partial protection, the Centers for Disease Control and Prevention also recommend additional concomitant meningococcal antibiotic prophylaxis (cdc.gov/meningococcal).

Screening and treatment for latent diseases should be performed prior to or concomitant with the initiation of immunosuppression.

- For most patients, screen for hepatitis B and C, human immunodeficiency virus (HIV), syphilis, and tuberculosis.
- For patients from a tropical climate, screen for *Strongyloides*.

Prophylactic therapies

- Prophylactic antibiotic against *Pneumocystis* infection should be considered in all patients receiving high-dose glucocorticoid (GC) or other immunosuppressants:
  - Trimethoprim-sulfamethoxazole is preferred.
  - Dapsone is second line (risk for anemia; must check glucose-6-phosphate dehydrogenase).
  - Atovaquone or pentamidine may be used in patients with sulfa-allergy.
- Spontaneous bacterial peritonitis may occur in nephrotic patients with ascites. Empiric antibiotics should include benzylpenicillin (pneumococcal infection).
- In recurrent spontaneous bacterial peritonitis, consider monthly IVIg 400 mg/kg daily × 4 days to keep serum IgG greater than 600 mg/dL (limited evidence).

NEPHRITIC GLOMERULAR DISORDERS AND VASCULITIS/VASCULOPATHY

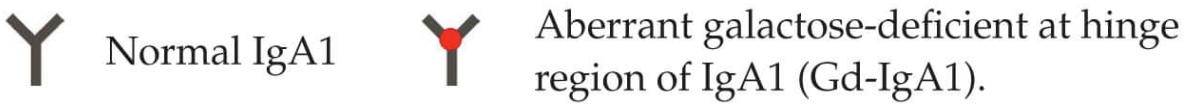
Immunoglobulin A Nephropathy (IgAN)

Background

- Most common GN worldwide
- Highest incidence in East Asians and Hispanics, followed by Caucasians; rare in individuals of African ancestry
- Comprises 10% to 20% of end-stage kidney disease (ESKD) due to high prevalence

Pathogenesis (four-hit model)

1. Production of aberrant galactose-deficient IgA1 (Gd-IgA1) by plasma cells



2. Autoantibodies (shown in green) directed against the underglycosylated hinge region of Gd-IgA1 are produced.

IgA and/or IgG autoantibodies combine with Gd-IgA1 to form circulating immune complexes (ICs).

3. Circulating IC deposit in the glomerular mesangium
4. Mesangial IC deposition activates complement and other inflammatory pathways, which then leads to mesangial cell proliferation, matrix deposition, glomerular injury, and tubulointerstitial fibrosis.

Clinical manifestations

IgAN has a peak incidence in the second and third decades of life but may occur at any age.

Hematuria with or without proteinuria

- Asymptomatic hematuria and proteinuria (incidental finding) occur in one-third of cases. This is more commonly seen in adults.
- Episodic macroscopic "gross" hematuria
  - Gross hematuria is more commonly seen in younger patients. Approximately half of patients with IgAN present with one or more episodes of gross hematuria, typically following an upper respiratory infection or gastroenteritis. Gross hematuria for the first time in individuals older than 40 years of age is rarely due to IgAN.
  - Gross hematuria may occur concurrently or within 3 days of onset of infection. Note faster onset following an inciting infection compared with postinfectious GN (PIGN).
  - Typically resolves by 3 days
  - Hematuria may be accompanied by flank or loin pain.

Proteinuria: nonnephrotic to nephrotic range and NS (<10%)

Disease progression

- Slowly progressive chronic kidney disease (CKD): 15% to 25% reach ESKD within 10 years, and 20% to 40% by 20 years
- AKI: may be associated with tubular obstruction from severe hematuria
- Rapidly progressive glomerulonephritis (RPGN) (crescentic IgAN) is uncommon.

Conditions associated with IgAN

IgAN may present in association with conditions involving organs that produce or clear IgA.

- Skin: dermatitis herpetiformis, psoriasis, psoriatic arthritis
- Liver: alcoholism, primary biliary cirrhosis, cirrhosis; hepatitis B, chronic schistosomiasis. Cirrhotic liver has reduced capacity to metabolize/clear IgA.
- Gastrointestinal (GI) tract: Crohn disease, ulcerative colitis, celiac disease
- Pulmonary: sarcoidosis, idiopathic hemosiderosis, cystic fibrosis, bronchiolitis obliterans, antineutrophil cytoplasmic autoantibody (ANCA) disease involving upper respiratory tract
- Neoplasia: lung, larynx, pancreas, mycosis fungoides
- Infection: HIV, leprosy, tuberculosis

- Systemic or immunologic disorders: systemic lupus erythematosus (SLE), rheumatoid arthritis, cryoglobulinemia, ankylosing spondylitis, Sjögren, Behçet, Reiter, familial immune-mediated thrombocytopenia, autoantibody IgA-mediated Goodpasture

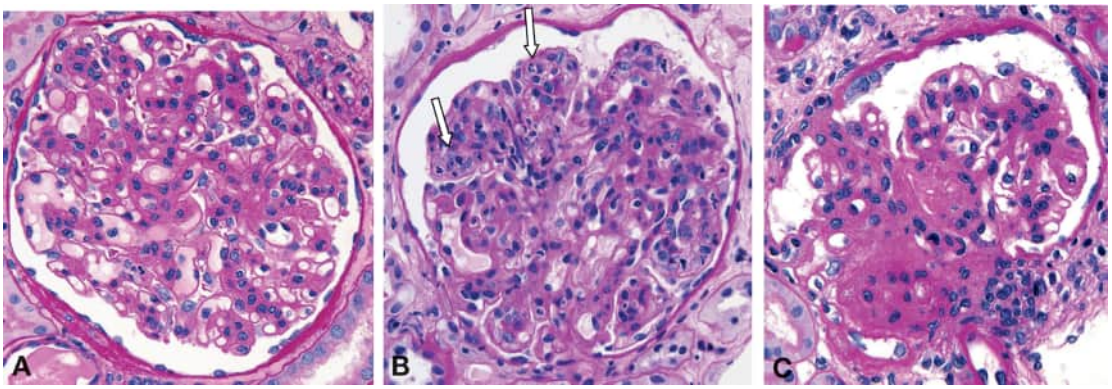
Primary systemic IgA vasculitis (IgAV) (a.k.a. Henoch-Schönlein purpura)

- IgAV usually occurs in the first decade of life but may occur at any age.
- Children: Ankara 2008 composite IgAV classification requires:
  - Purpura or petechiae with lower limb predominance, and
  - At least one of the following four criteria: (1) abdominal pain, (2) histopathology, (3) arthritis or arthralgia, or (4) renal involvement
  - 100% sensitivity and 87% specificity for IgAV
- Adults: The American College of Rheumatology (1990) published criteria for IgAV.
  - Requires at least two of the following: (1) age 20 years or below at disease onset, (2) palpable purpura, (3) acute abdominal pain, or (4) skin or bowel wall biopsy showing granulocytes in the walls of small arterioles/venules
  - 87.1% sensitive and 87.7% specific for IgAV
- Patients with IgAV should be screened for malignancy and other secondary causes.

Diagnosis of IgAN

- Diagnosis is by kidney biopsy.
- Currently, there are no validated surrogate diagnostic or prognostic markers.

Histology (Figure 7.1):



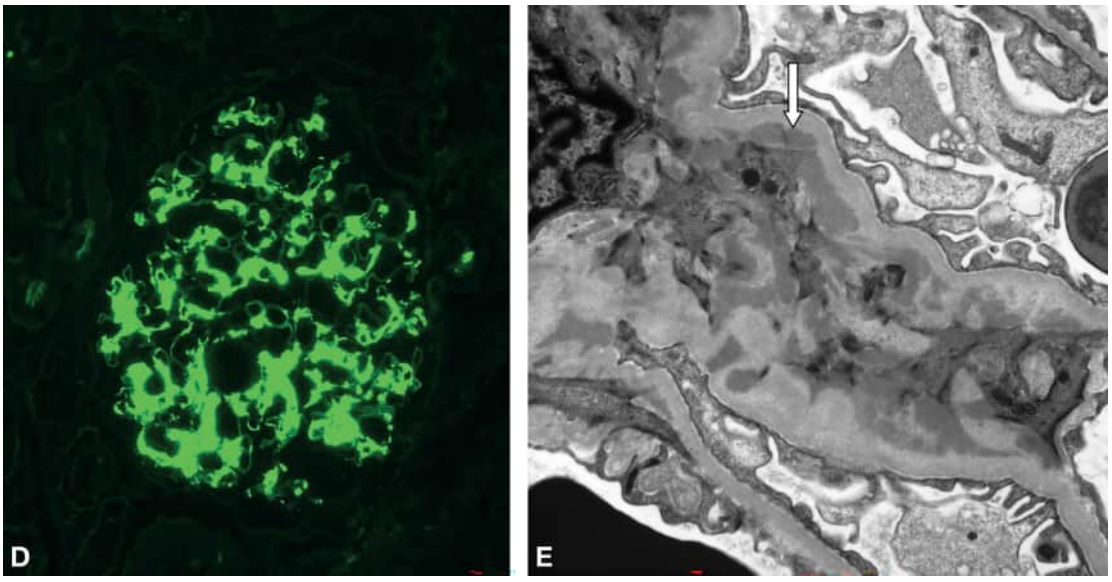


FIGURE 7.1 Immunoglobulin A (IgA) nephropathy. A. Global mesangial hypercellularity (M1 lesion) (periodic acid-Schiff ×400). B. Endocapillary hypercellularity with luminal occlusion (arrows) (E1 lesion) (periodic acid-Schiff ×400). C. Mesangial hypercellularity and segmental glomerulosclerosis (M1 and S1 lesions) (periodic acid-Schiff ×400). D. Global mesangial IgA (×275). E. Mesangial electron-dense deposits, prominent in the paramesangial region (arrow) with a single subepithelial deposit (×14,000).

Light microscopy (LM): mesangial expansion and hypercellularity, with or without segmental and/or global glomerulosclerosis, endocapillary hypercellularity, crescents
Immunofluorescence (IF) microscopy: dominant or co-dominant mesangial IgA deposits

- ±IgG, IgM, and/or C3
- ±Light-chain (LC) deposition (typically λ)

Electron microscopy (EM): mesangial electron-dense deposits and/or few small scattered subendothelial deposits, rare subepithelial deposits
"MEST-C" OXFORD Classification for IgAN:

- **M**esangial hypercellularity (>3 cells in one or more mesangial areas) in more than 50% glomeruli = M1, otherwise = M0
- **E**ndocapillary hypercellularity one or more glomeruli = E1, otherwise E0
- **S**egmental sclerosis or adhesion in one or more glomeruli = S1, otherwise S0
- **T**ubular atrophy and interstitial fibrosis involving 0% to 25%, 26% to 50%, or more than 50% of renal cortex = T0, T1, T2, respectively
- **C**rescents**:** C0 = no crescent; C1 = active (cellular/fibrocellular) crescent in at least one glomerulus but less than 25% of glomeruli; C2 = active crescents in 25% or more glomeruli

Clinical significance of MEST-C classification

- MEST-C classification predicts renal outcome: M1, S1, ≥T1, and ≥C1 are associated with worse prognosis; M1, S1 and T1/T2 are additive.
- MEST-C is not used to guide treatment or predict treatment response.
- IgAV outcome is associated with E1.

Prognostic indicators

- Presenting factors that portend worse prognosis for IgAN: proteinuria greater than 1 g/d, HTN (diastolic blood pressure [DBP] ≥95 mm Hg or antihypertensive therapy), persistent hematuria, SCr 1.5 mg/dL or more, histologic findings with greater MEST-C scores
- A calculator for disease progression based on the IgAN International Prediction Tool can be found on the Calculate by QxMD website.
- The calculator predicts the risk of 50% decline in estimated GFR (eGFR) or ESKD after a landmark time based on clinical and histologic variables at the time of kidney biopsy including eGFR, BP, proteinuria, age, race/ethnicity (White, Japanese, Chinese, or other), prior use of ACEi/ARB, Oxford MEST-C histology scores, and immunosuppression use at or prior to biopsy.
- This risk stratification tool does not predict responses to any particular treatment.

Management of IgAN

Table 7.3 summarizes management strategies for patients with IgAN.

Table 7.3 Management strategies for patients with IgA nephropathy (IgAN) per KDIGO 2021

IgAN conditions	Management
Any form of IgAN with proteinuria	• SBP control <120 mm Hg as safely tolerated • ACEi/ARB is *recommended* for proteinuria >0.5 g/d ± HTN. • MRA may be added for antiproteinuric and antifibrotic effects. • SGLT2i may be indicated for maximal supportive care. • Consider sparsentan (dual ARB and ETAR) if at risk for progression + persistent proteinuria ≥1 g/d despite ACEi/ARB + SGLT2i. • IST is contraindicated for eGFR <30 mL/min/1.73 m^2 with evidence of advanced and irreversible kidney injury. • Consider tonsillectomy if recurrent tonsillitis.

Primary IgAN	• Consider IST options below if high CKD progression risk (persistent proteinuria >0.75-1 g/d despite maximal supportive care for ≥90 d).
	  • Systemic GC: 6-mo course of corticosteroid (weak evidence)
	  • Targeted-release budesonide: Consider in patients at risk of rapid disease progression, defined as having uPCR >1.5 g/g Cr or proteinuria >2 g/d, who cannot take systemic GC for whatever reason.
	  • MMF: may be beneficial in a small Chinese RCT (limited data)
	  • Hydroxychloroquine: reduced proteinuria in a small Chinese RCT in patients with persistent proteinuria despite maximum ACEi/ARB
	  • Consider enrollment in clinical trial.

IgAN with AKI and macroscopic hematuria	• Consider tubular obstruction with RBCs and/or acute tubular injury. • Consider repeat kidney biopsy if AKI persists for ≥2 wk to rule out crescentic IgAN.
Secondary IgAN	• Evaluate and treat secondary causes (eg, inflammatory bowel disease).
IgAN + MCD	• Treat as minimal change.

IgAN conditions	Management
Rapidly progressive crescentic IgAN	• Crescentic glomeruli with mesangial and endocapillary hypercellularity ± segmental focal necrosis, and ≥50% decline in eGFR over ≤3 mo in the absence of other causes of RPGN. • Treat with CYC and GC (similar to ANCA-associated vasculitis).
IgA vasculitis (IgAV)	• If high risk for CKD progression despite supportive care, treat with GC. • For patients with IgAV, associated RPGN, and life-threatening complications, adding plasma exchange to GC may accelerate recovery. More data are needed.
IgAN in pregnancy planning	• For patients with high CKD progression risk, consider a 6-mo course of immunosuppression to optimize proteinuria prior to conception.
IgAN in children	• Most pediatric nephrologists treat children with proteinuria >1 g/d and mesangial hypercellularity (Oxford M1) with ACEi/ARB + GC. • Consider GC and oral CYC in children with rapidly progressive IgAN.

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ETAR, endothelin 1 type A receptor; GC, glucocorticoid; HTN, hypertension; IST, immunosuppressive therapy; KDIGO, Kidney Disease: Improving Global Outcomes; MCD, minimal change disease; MMF, mycophenolate mofetil; MRA, mineralocorticoid receptor antagonist; RBCs, red blood cells; RCT, randomized controlled trial; RPGN, rapidly progressive glomerulonephritis; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein-to-creatinine ratio.

Supportive care

- Healthy lifestyle modifications per routine American College of Cardiology/American Heart Association (ACC/AHA) HTN guidelines
- ACEi or ARB is recommended if proteinuria is greater than 0.5 g/d whether or not HTN is present; Otherwise, ACEi/ARB is *suggested*.
- Mineralocorticoid receptor antagonists may also be considered for antiproteinuric and antifibrotic effects.
- Sodium/glucose cotransporter 2 inhibitors (SGLT2i) may be indicated for maximal supportive care in patients with IgAN and proteinuria.
  - DAPA-CKD trial including 270 patients with IgAN revealed 4% versus 15% reaching primary composite end point of sustained decline in eGFR of 50% or more, ESKD, or death from kidney disease–related or CV cause in patients receiving dapagliflozin versus placebo, respectively.
  - EMPA-KIDNEY trial involving 6,609 patients showing a lower risk of progression of kidney disease or death from CV causes compared with placebo also included 817 patients with IgAN.
- Sparsentan
  - Sparsentan is a dual angiotensin II receptor subtype 1 and endothelin type A receptor antagonist that was evaluated in PROTECT-2, a phase 3 trial in which over 400 adults with IgAN and persistent proteinuria despite 3 months of optimized supportive care were randomly assigned to sparsentan or irbesartan once daily. At week 110, patients receiving sparsentan had a greater reduction in proteinuria and

a smaller decline in eGFR. Adverse effects including hypotension, dizziness, and AKI were more frequent with sparsentan.

- Sparsentan was U.S. Food and Drug Administration (FDA) approved in February 2023 to treat patients with IgAN who are at risk for progression. It may be considered an alternative option to reduce proteinuria in patients with IgAN and persistent proteinuria 1 g/d or greater despite optimal treatment with an ACEi/ARB and SGLT2i.

- Consider tonsillectomy if recurrent tonsillitis.

IST considerations for primary IgAN

- IST is contraindicated in patients with evidence of advanced and irreversible kidney injury (eg, eGFR <30 mL/min/1.73 m^2 for ≥3 months or small kidneys with cortical thinning).
- Consider IST for patients with high risk of CKD progression (eg, persistent proteinuria >0.75-1 g/d despite maximal supportive care for ≥90 days).
- Caveat regarding IST for patients with IgAN: The presence of crescents in the kidney biopsy is not an automatic indication for starting immunosuppression in the absence of concomitant functional change.

Immunosuppressive therapeutic options for IgAN

- Systemic GCs (prednisone, methylprednisolone): Consider a 6-month course of corticosteroid (weak evidence).
  - Initial high-dose prednisone (eg, 0.8-1.0 mg/kg/d up to 75 mg daily) is maintained for 2 months (8 weeks), followed by taper of 5 to 10 mg every 2 weeks for a total exposure of 6 to 8 months.
  - Limitations of GC:
    - Proteinuria reduction has been shown with short-term (3 years) follow-up; however, long-term benefits greater than 7 years regarding eGFR loss, ESKD, or death with the use of GC have not been shown.
    - Significant adverse effects: GC should be avoided in patients with relative contraindications, including diabetes mellitus (DM), obesity, latent infections, secondary IgAN, uncontrolled psychiatric illness, or a history of upper GI bleed.
- Targeted-release formulation of the GC budesonide (TRF-budesonide):
  - An oral formulation of budesonide designed to be released at the distal ileum where mucosal B lymphocytes within Peyer patches are postulated to produce Gd-IgA1.
  - TRF-budesonide has been shown to reduce proteinuria and slow eGFR decline.
  - TRF-budesonide is FDA approved for the reduction of proteinuria in patients with IgAN at risk of rapid disease progression, defined as having uPCR greater than 1.5 g/g and proteinuria greater than 2 g/d.
  - May be considered in patients who cannot tolerate or do not wish to take oral systemic GCs
- Mycophenolate mofetil (MMF)
  - Limited data: beneficial in small Chinese randomized controlled trial (RCT) study
  - Some experts consider using MMF in high-risk patients or those not tolerating GC.

- Hydroxychloroquine (HC): Small Chinese RCT involving patients with persistent proteinuria despite maximum ACEi/ARB showed proteinuria reduction.
- Given weak data on long-term benefits of GC in patients with IgAN, consider enrollment in clinical trial if applicable.
- Investigational agents:
  - Inhibitors of IC-mediated complement activation (eg, iptacopan, avacopan, narsoplimab, ravulizumab)
  - Inhibitors of B-cell–activating factor (BAFF) and APRIL (a proliferation-inducing ligand): Both BAFF and APRIL are tumor necrosis factor (TNF) family ligands involved in B-cell and plasma cell function and survival, and the pathogenesis of autoimmune diseases including IgAN (eg, blisibimod, atacicept, telitacicept, sibeprenlimab).
  - Plasma cell– and B-cell–depleting agents (eg, felzartamab, bortezomib)

Management considerations for IgAN variants

IgAN with AKI and macroscopic hematuria: may be related to tubular obstruction with RBCs and/or acute tubular injury. However, consider repeat kidney biopsy if AKI persists for 2 weeks or more to rule out crescentic IgAN.
Secondary IgAN: Evaluate and treat secondary causes (ie, conditions associated with IgAN).
Nephrotic IgAN with apparent MCD on biopsy: Treat as MCD.
Rapidly progressive crescentic IgAN:

- Defined as mesangial and endocapillary hypercellularity, glomerular crescents often segmental focal necrosis, and 50% or more decline in eGFR over 3 months or less and in the absence of other causes of RPGN. Note that having crescents without eGFR decline does not define rapidly progressive IgAN. However, close follow-up is necessary.
- If no endocapillary or mesangial hypercellularity is present, testing for ANCA is recommended.
- Treat with cyclophosphamide (CYC) and GC similar to the treatment of ANCA-associated vasculitis (AAV). Rituximab (RTX) has not been shown to be effective in this IgAN subset.

IgA vasculitis:

- For patients at high risk for CKD progression despite maximal supportive care, treat with GC as outlined above for primary IgAN.
- For patients with IgAV, associated RPGN, and life- or organ-threatening extrarenal complications, the addition of plasma exchange (PLEX) to GC therapy may help accelerate recovery in uncontrolled small case series. More data are needed.

IgAN in pregnancy planning: For patients with high CKD progression risk, consider a 6-month course of immunosuppression to optimize proteinuria prior to conception.
IgAN in children:

- Most pediatric nephrologists treat children with proteinuria greater than 1 g/d and mesangial hypercellularity (Oxford M1) with ACEi/ARB plus GC.

- Children with rapidly progressive IgAN have poor outcome. GC plus oral CYC may be considered.

RENAL AND SYSTEMIC VASCULITIDES

Classification of Vasculitides (Figure 7.2)

Large-sized vessels: Aorta and large branches including renal artery

Granulomatous arteritis: giant cell or Takayasu arteritis (**Table 7.4**)

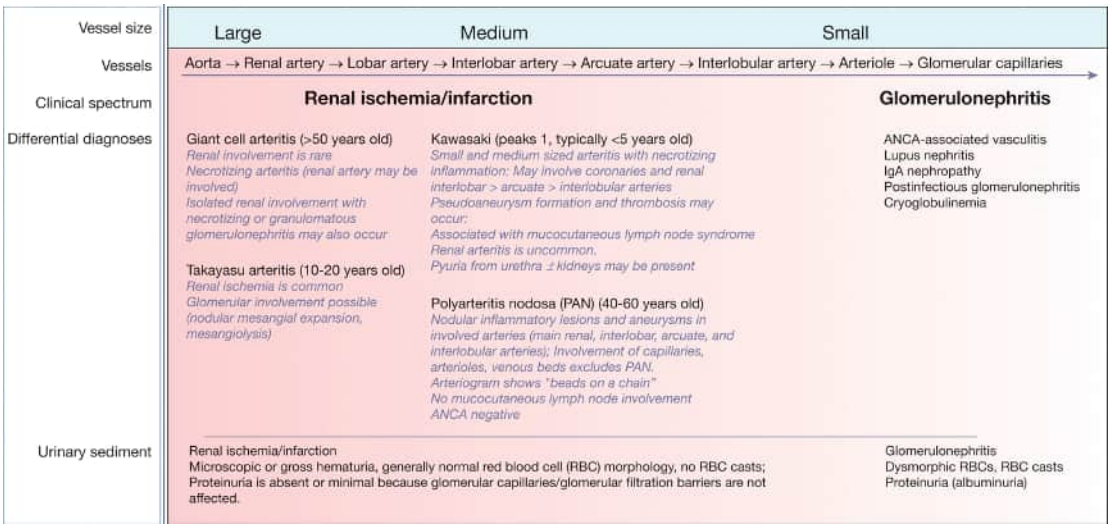

Vessel size
Large
Medium
Small
Vessels
Aorta → Renal artery → Lobar artery → Interlobar artery → Arcuate artery → Interlobular artery → Arteriole → Glomerular capillaries
Clinical spectrum
Renal ischemia/infarction
Glomerulonephritis
Differential diagnoses
Giant cell arteritis (>50 years old)
Renal involvement is rare
Necrotizing arteritis (renal artery may be involved)
Isolated renal involvement with necrotizing or granulomatous glomerulonephritis may also occur
Takayasu arteritis (10-20 years old)
Renal ischemia is common
Glomerular involvement possible (nodular mesangial expansion, mesangiolysis)
Kawasaki (peaks 1, typically <5 years old)
Small and medium sized arteritis with necrotizing inflammation: May involve coronaries and renal interlobar > arcuate > interlobular arteries
Pseudoaneurysm formation and thrombosis may occur:
Associated with mucocutaneous lymph node syndrome
Renal arteritis is uncommon.
Pyuria from urethra ± kidneys may be present
Polyarteritis nodosa (PAN) (40-60 years old)
Nodular inflammatory lesions and aneurysms in involved arteries (main renal, interlobar, arcuate, and interlobular arteries); Involvement of capillaries, arterioles, venous beds excludes PAN.
Arteriogram shows "beads on a chain"
No mucocutaneous lymph node involvement
ANCA negative
ANCA-associated vasculitis
Lupus nephritis
IgA nephropathy
Postinfectious glomerulonephritis
Cryoglobulinemia
Urinary sediment
Renal ischemia/infarction
Microscopic or gross hematuria, generally normal red blood cell (RBC) morphology, no RBC casts; Proteinuria is absent or minimal because glomerular capillaries/glomerular filtration barriers are not affected.
Glomerulonephritis
Dysmorphic RBCs, RBC casts
Proteinuria (albuminuria)

FIGURE 7.2 Clinical spectrum of vasculitides and associated kidney lesions.
Abbreviations: ANCA, antineutrophil cytoplasmic antibody; IgA, immunoglobulin A; RBC, red blood cell.

Table 7.4 Large-sized vasculitis: Giant cell versus Takayasu arteritis

Large-sized vasculitis	Giant cell arteritis	Takayasu arteritis
Age of onset	Typically >50 year old	10-40 year old; very rare after age 50
Gender	Female:male: 4:1	Female:male: 9:1 (predominantly Asians)
Pathogenesis	Unclear: Thought to involve genetics, sex, and age-related alterations of the immune and arterial systems	Unclear: Presumed autoimmune disease triggered by bacteria, viruses, or tuberculosis followed by an autoimmune process driven by molecular mimicry
Clinical manifestations and diagnosis	Manifestations: Headaches, temporal artery tenderness, blindness, deafness, jaw claudication, tongue dysfunction, reduced pulses, extremity claudication; hypertension may be possible. Laboratory findings: ±elevated ESR, CRP Diagnosis: Temporal artery biopsy	Manifestations: Reduced pulses, vascular bruits, claudication, renal ischemia due to renal artery stenosis or aortic coarctation; hypertension possible Laboratory findings: ±elevated ESR, CRP Diagnosis: MRA or CTA of head and neck, chest, and abdomen showing smoothly tapered luminal narrowing or occlusions of large arteries

Large-sized vasculitis	Giant cell arteritis	Takayasu arteritis
Pathology	Renal arteries may be involved but significant disease is rare. Very rare isolated renal involvement with necrotizing or granulomatous glomerulonephritis may occur.	Ischemic renal disease relatively common; glomerular lesion possible: nodular mesangial matrix expansion, mesangiolysis
Treatment	GC ± tocilizumab or MTX for GC sparing or intolerance	GC ± GC-sparing agent (eg, MTX, AZA, MMF)

Abbreviations: AZA, azathioprine; CRP, C-reactive protein; CTA, computed tomography angiogram; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; MMF, mycophenolate mofetil; MRA, magnetic resonance angiogram; MTX, methotrexate.

Giant cell arteritis typically occurs in patients older than 50 years of age. Renal arteries may be involved, but significant disease is rare. If isolated renal involvement with necrotizing or granulomatous GN occurs, this is likely concomitant ANCA vasculitis.

Takayasu arteritis typically occurs in patients younger than 50 years of age. Ischemic renal disease is relatively common. Glomerular involvement is possible (nodular mesangial expansion, mesangiolysis).

Medium-sized vessels: Main renal, interlobar, arcuate arteries

Necrotizing arteritis: Kawasaki disease, polyarteritis nodosa (PAN) (**Table 7.5**)

Kawasaki disease in children (peaks at age 1 year, typically <5 years)

Table 7.5 Medium-sized vasculitis: Polyarteritis nodosa versus Kawasaki arteritis

Medium-sized vasculitis	Polyarteritis nodosa (PAN)	Kawasaki
Age of onset	40-60 year old	Peaks at age 1, typically <5 year old
Epidemiology	Male to female: 1.5:1	Asians and Polynesians > Caucasians and Blacks Sporadic; occasional endemic or epidemic pattern
Pathogenesis	Unknown; idiopathic or associated with drugs, HBV, HCV, hairy cell leukemia	Both cell- and antibody-mediated mechanisms possible; possible precipitating factors: infection or environmental toxin
Clinical manifestations and diagnosis	ACR criteria: Having a radiographic or pathologic diagnosis of vasculitis and ≥3 of the following: (1) weight loss ≥4 kg, (2) livedo reticularis, (3) testicular tenderness, (4) myalgia or leg weakness/tenderness, (5) mononeuropathy or polyneuropathy, (6) DBP >90 mm Hg, (7) elevated BUN or SCr unrelated to dehydration or obstruction, (8) HBsAg or HBsAb, (9) arteriogram with aneurysms or occlusions of visceral arteries, (10) positive PMN in small-/medium-sized artery No mucocutaneous lymph node involvement	Mucocutaneous lymph node syndrome: Fevers, mucosal inflammation, swollen red (strawberry) tongue, polymorphous erythematous rash, indurative edema of extremities, erythema of palms/soles, desquamation from tips of digits, conjunctival injection, lymphadenopathy, coronary arteritis (possible myocardial infarction) Renal arteritis is uncommon. Disease is typically self-limited, lasting on average 12 d without therapy.

Medium-sized vasculitis	Polyarteritis nodosa (PAN)	Kawasaki
Histopathology	Necrotizing vasculitis involving renal, interlobar, arcuate, rarely interlobular arteries; involvement of capillaries, arterioles, venous beds excludes PAN. Nodular inflammatory lesions and aneurysms in arteries Acute arterial lesion: Segmental transmural fibrinoid necrosis ± leukocyte infiltration; chronic changes: arterial wall erosions from necrotizing inflammation into surrounding perivascular tissues leading to appearance of enlarged lumen, hence "pseudoaneurysm" and propensity for thrombosis and rupture	Medium and less often small-vessel arteritis with necrotizing inflammation, frequently involving coronaries and renal arteries (interlobar > arcuate > interlobular arteries) Pseudoaneurysm formation and thrombosis may occur.
Treatment	If HBV or HCV: antiviral therapy ± corticosteroid or PLEX depending on severity pending response to antiviral therapy If no hepatitis B or C: GC ± cytotoxic agent (eg, CYC), based on disease severity	Aspirin and intravenous Ig therapy ± corticosteroids Recurrence is rare if promptly treated.

Abbreviations: BUN, blood urea nitrogen; CYC, cyclophosphamide; DBP, diastolic blood pressure; GC, glucocorticoid; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; PMN, polymorphonuclear neutrophil; SCr, serum creatinine.

- Involves inflammation of oral nasal mucosa (eg, mouth, nose, throat) and lymph nodes, known as mucocutaneous lymph node (MCLN) syndrome. Symptoms include fevers, mucosal inflammation, swollen red (strawberry) tongue, polymorphous erythematous rash, indurative edema of extremities, erythema of palms/soles, desquamation from tips of digits, conjunctival injection, lymphadenopathy, and coronary arteritis with possible myocardial infarction (MI).
- Renal arteritis is uncommon.
- Sterile pyuria from urethra and/or kidneys may be present.

PAN occurs more commonly in adults aged 40 to 60 years *without* MCLN.

- Involvement of capillaries, arterioles, and venous beds excludes PAN.
- Nodular inflammatory lesions and aneurysms in arteries
- Microaneurysms in PAN may resemble "beads on a chain" on angiogram (see **Figure 5.2** in **Chapter 5: Hypertension**).

Small-sized vessels: Interlobular arteries, arterioles, glomerular capillaries

Vasculitides with IC deposition in vessel walls

- Cryoglobulinemia: Cryoglobulin deposits often affect both skin and glomeruli.
- IgA-dominant deposits (IgAV): vasculitis involving skin, gut, and glomeruli with associated arthritis/arthralgias
- SLE or rheumatoid arthritis
- Others: postinfectious, hypocomplementemic urticarial (anti-C1q) vasculitis

Vasculitides with paucity of IC deposition in vessel walls

- Granulomatosis polyangiitis (GPA, formerly known as Wegener), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly

known as Churg-Strauss). These conditions are characterized by:

- Necrotizing inflammation of small vessels (ie, arterioles, capillaries, and venules). Capillary inflammation includes necrotizing and crescentic GN and medullary angiitis.
- Typically associated with ANCA

- Collectively, these are referred to as AAV
- Necrotizing and crescentic GN may occur with or without extrarenal manifestations in patients with AAV. **Table 7.6** summarizes the clinical features of AAV.

Table 7.6 Clinical manifestations of ANCA-associated vasculitis syndromes

ANCA-associated vasculitis syndromes	**MPA 30%-50% PR3-ANCA 50%-60% MPO-ANCA 10%-30% negative ANCA**	**GPA 75%-90% PR3-ANCA 10%-20% MPO-ANCA 5%-10% negative ANCA**	**EGPA 5%-10% PR3-ANCA 40%-50% MPO-ANCA 30%-50% negative ANCA**	**[a]Renal limited vasculitis 10%-20% PR3-ANCA 70%-90% MPO-ANCA 10% negative ANCA**
Patient characteristics	Typically present in the fifth to eighth decades of life, with MPO-ANCA in the older age range Slight male predominance; more common in White than Black			
Lungs	Necrotizing vasculitis without granulomatous inflammation	Necrotizing **G**ranulomatous inflammation; sinusitis, rhinitis, otitis media, lung nodules/cavitation, saddle nose, ocular lesions more specific with PR3-ANCA	Asthma; **E**osinophil-rich and **G**ranulomatous inflammation	ANCA-positive glomerulonephritis without any classic systemic symptomology for MPA, GPA, or EGPA
Kidneys	Often rapidly progressive disease but can be indolent or chronic; PR3-ANCA tends to be more acute in presentation compared with more indolent chronic presentation with MPO-ANCA.		Kidney disease is less frequent and less severe compared with MPA and GPA.	
Gastrointestinal tract	50% of patients with MPA, GPA, or EGPA may present with abdominal pain, bloody stool with mesenteric ischemia/intestinal infarction, pancreatitis, hepatitis.			
Skin	Nodular cutaneous lesions (rare)	Skin nodules due to dermal or subcutaneous arteritis and necrotizing granulomatous infiltration		
Neurologic	Peripheral neuropathy, usually mononeuritis multiplex Up to 70% in EGPA, 50% GPA, 30% MPA CNS involving meninges may occur (less common).			
Other organs	20% cardiac (eg, heart block, ventricular hypokinesis)		Eosinophilia cardiac infiltration (50%)	

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; EGPA, eosinophilic granulomatous polyangiitis; GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

[a]Drug-induced AAV may also more commonly present with MPO-ANCA. In addition, positivity for both PR3 and MPO-ANCA is not uncommon with drug-induced AAV.

ANCA and ANCA-Associated Vasculitis

- ANCA are antineutrophil cytoplasmic **autoantibodies** directed against various lysosomal enzymes that act as **antigens**.

ANCA may direct against various antigens including:

- Proteinase 3 (PR3), myeloperoxidase (MPO), and other "atypical" antigens (eg, human neutrophil elastase, lysozyme)
- The pathogenic role of atypical ANCAs is unclear.

Cytoplasmic (c-ANCA) and perinuclear (p-ANCA)

- c-ANCA and p-ANCA refer to the IF staining pattern in ethanol-permeabilized neutrophils exposed to patient's serum. All antigens (including MPO) are cytoplasmic in vivo. With ethanol preparation, MPO migrates around cell nuclei, resulting in a perinuclear (p-ANCA) staining pattern. PR3 remains in cell cytoplasm, causing a cytoplasmic (c-ANCA) staining pattern. C-ANCA and p-ANCA can bind to proteinases other than PR3 and MPO that are not necessarily pathogenic.
- High-quality enzyme immunoassay (EIA) for PR3 and MPO-ANCA is the preferred screening method for AVV. However, this will not detect atypical ANCAs.

Notes regarding ANCA

ANCA-negative MPA, GPA, and necrotizing and crescentic GN

- 10% of patients presenting with signs and symptoms of MPA, GPA, or necrotizing and crescentic GN are persistently ANCA negative.
- Treatment of these patients is similar to those with positive ANCA.

Coexistence of ANCA and anti-glomerular basement membrane (GBM) antibodies

- In a single-center study from the United Kingdom in 2004, 5% of patients with ANCA-positive sera also had anti-GBM antibodies and 32% of patients with anti-GBM had detectable ANCA.
- When ANCA and anti-GBM antibodies coexist, the disease course is similar to anti-GBM disease in early disease, but the relapse pattern is similar to ANCA disease.

AVV associated with the use of cocaine adulterated with levamisole

- Most affected patients present with ANCA against both MPO and PR3.
- ANCA may be directed against other autoantigens, including antinuclear antibody (ANA), lupus anticoagulant, anticardiolipin, anti-double-stranded DNA (dsDNA), and others.
- Patients may present with purpuric to necrotic skin lesions, often earlobes and nose.
- Renal manifestations may include crescentic GN or renal infarction.

Classic PAN is usually ANCA negative.

Proposed pathogenesis of ANCA vasculitis

1. Priming of neutrophils by cytokines (eg, from a viral infection) *leads to*:
2. Increased neutrophil expression/trafficking of ***ANCA antigens*** (eg, PR3 or MPO) onto cell surfaces, where they are exposed to ANCA.
3. The **ANCA**: **ANCA-antigen** interaction in cytokine-primed neutrophils *leads to*:
   a. Neutrophil release of enzymes from granules, toxic oxygen metabolites, inflammatory mediators into surroundings AND
   b. Adherence of activated neutrophils to endothelial cells, *BOTH leading to*:
4. Endothelial cell injury, vascular thrombosis, and surrounding tissue ischemia, necrosis

Clinical manifestations (see **Table 7.6** for specific manifestations of different AAV)

- ANCA-associated GN may present with nonnephrotic proteinuria and hematuria, acute nephritis, RPGN, or slowly progressive nephritis.
- Nonspecific signs and symptoms of necrotizing vasculitis: cutaneous purpura, papular/ulcerated lesions, peripheral neuropathy (mononeuritis multiplex), nonspecific muscular/joint pain, evidence of GI bleed, tendency for venous thrombosis

Histopathology and classification of AAV

- Necrosis and/or crescents, which are often in different stages simultaneously (cellular, fibrocellular, fibrotic) due to the relapsing nature of the disease (**Figures 7.3**). Active arteritis is seen in approximately 15% of biopsies. There are four histologic classes:

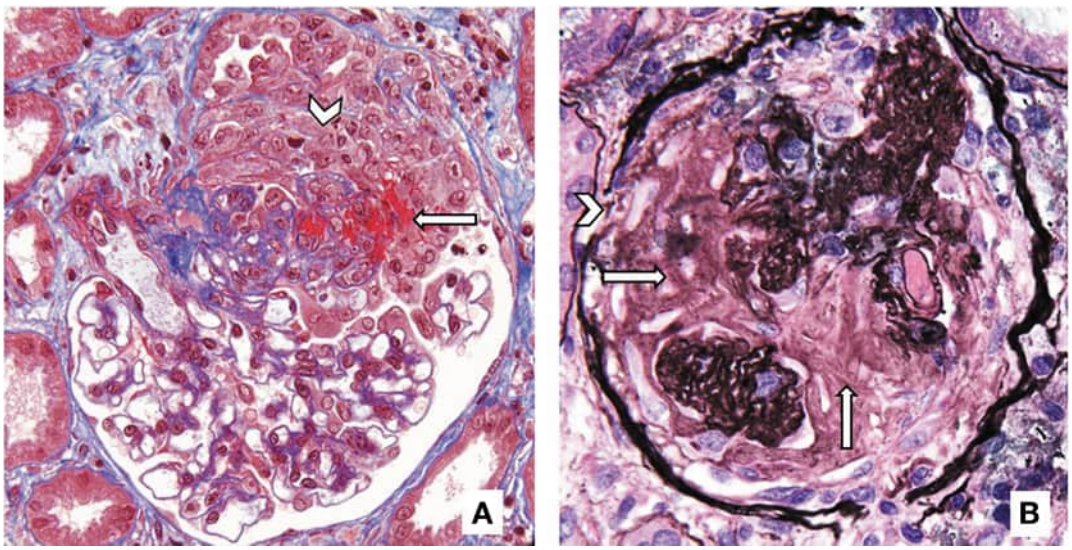


FIGURE 7.3 Glomerular crescents in antineutrophil cytoplasmic antibody–associated vasculitis. A. Necrotizing and cellular (active) crescent. There is segmental necrosis with capillary disruption and urinary space fibrin (arrow) and inflammatory and epithelial cells in the urinary space (arrowhead) (Masson trichrome ×400). B. Fibrotic (chronic) crescent. There is collagen in the urinary space (arrows) separating the obliterated glomerular tufts with a break in Bowman capsule (arrowhead) (Jones silver ×400).

- Sclerotic class: 50% or more globally sclerotic glomeruli
- Focal class: 50% or more normal glomeruli

- Crescentic class: 50% or more cellular (defined as cellular and fibrocellular) crescents
- Mixed class (ie, all histologic characteristics in <50% of glomeruli)

IST for AAV

Dosing for induction and maintenance therapies, PLEX, and GC for AAV based on KDIGO 2024 are provided in **Appendix A7.1**

Induction therapy for new-onset AAV with renal involvement

For patients without organ-threatening disease

- Combination of RTX plus (GC taper or avacopan) or combination of CYC plus (GC taper or avacopan) is recommended as initial induction therapy. See information on avacopan below.
- Preferential selection of CYC versus RTX is summarized in **Table 7.7** (KDIGO 2024).

Table 7.7 Induction therapy for ANCA-associated vasculitis (KDIGO 2024)

[a]Induction therapy of ANCA-associated vasculitis	
For patients without organ-threatening disease	• Combination of RTX + (GC taper or avacopan) or • Combination CYC + (GC taper or avacopan) is recommended as initial induction therapy.
Preferential selection of CYC vs RTX as primary induction	
Rituximab is preferred for the following:	Cyclophosphamide is preferred for the following:

• PR3-ANCA disease
• Relapsing disease
• Patients with serum creatinine <4 mg/dL
• Fertility concerns for children, men, or women
• Frail older patients
• Steroid-sparing protocol is a high priority.
• Immunoglobulin G (IgG) levels <300 mg/dL may predict greater risks for secondary immunodeficiency with RTX. IgG levels should be measured at baseline and every 6 mo for patients on RTX.
	• Rituximab is difficult to access
	• Patients with markedly reduced kidney function, ie, creatinine ≥4 mg/dL or rapidly declining GFR: Combination of RTX and CYC can be considered as an alternative to 3-6 mo of CYC alone. This combination resulted in a similar rate of remission and adverse events as CYC in the RITUXVAS trial.
	• Route of administration for CYC:
	  • Intravenous (IV) is preferred to oral CYC in patients with preexisting moderate cumulative CYC dose, lower white blood cell counts, medical nonadherence, access to infusion center.
	  • Oral (PO) is preferred to IV CYC: cost, no access to infusion center, adherence is not an issue.

For patients with vital organ/life-threatening disease or SCr >3.4 mg/dL	• Combination of RTX + CYC or • Combination of CYC + (GC or avacopan) is recommended. • Consider plasma exchange (PLEX)
Immunosuppression for nonsevere disease	• Mycophenolate mofetil (MMF): Compared to CYC, no significant differences in outcome were found, but CYC tended to show better efficacy and fewer relapses.

[a]Induction therapy of ANCA-associated vasculitis

	• Methotrexate (MTX): Compared with CYC, MTX was associated with a higher relapse rate.

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CYC, cyclophosphamide; GC, glucocorticoid; KDIGO, Kidney Disease: Improving Global Outcomes.

[a]See **Appendix A7.1** for dosing.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 Clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int.* 2024;105(3S):S71-S116.

For patients with vital organ-/life-threatening disease or SCr greater than 3.4 mg/dL

- Combination of RTX plus CYC or combination of CYC plus (GC or avacopan) is recommended.
- Consider PLEX.

The use of GC with induction therapy

- IV methylprednisolone at 1 to 3 g total in patients with severe disease on presentation is not evidence based and is likely to contribute to GC toxicity.
- Oral GC with rapid over slow tapering is preferred due to minimal difference in achieving sustained remission. For the first week, the prednisolone dose is 1 mg/kg/d (50 mg/d for weight <50 kg, 60 mg/d for weight 50-75 kg, and 75 mg/d for weight >75 kg). Following CYC induction, oral prednisolone should be reduced to 5 mg/d by 6 months and, following RTX induction, withdrawn by 6 months.

Avacopan as an alternative to GC

- Avacopan (Tavneos), is a complement 5a receptor (C5aR) antagonist that can block C5a-mediated neutrophil activation and migration. The exact mechanism whereby avacopan exerts its therapeutic effect in patients with AVV remains to be definitively established.
- ADVOCATE trial involving 330 patients with AAV, 81% with renal involvement:
  - eGFR improved by an average of 7.3 versus 4.1 mL/min/1.73 m^2 at 52 weeks in the avacopan versus prednisone group.
  - In the subgroup of patients with eGFR 20 mL/min/1.73 m^2 or less, GFR improved by 16.1 versus 7.7 mL/min/1.73 m^2 at 52 weeks with avacopan versus prednisone.
- Avacopan may be considered in place of GC for induction therapy in combination with either RTX or CYC in patients with increased risk of GC toxicity (eg, high infection risk, DM, psychiatric disorders, osteoporosis).
- Avacopan is primarily metabolized by CYP3A4.

Immunosuppression for nonsevere disease

- MMF: Compared to CYC, no significant differences in outcome were found with MMF, but CYC tended to show better efficacy and fewer relapses.
- Methotrexate (MTX): Compared with CYC, MTX was associated with a higher relapse rate.

Plasma exchange

- 2022 meta-analysis confirmed that PLEX reduced kidney failure risk by 4.6% and 6% in patients with SCr between 3.4 and 5.7 mg/dL and greater than 5.7 mg/dL, respectively, at 12 months.
- Consider PLEX in patients with any of the following:
  - Severe renal impairment (SCr >3.4 mg/dL)
  - Diffuse pulmonary hemorrhage with hypoxemia
  - Concurrent anti-GBM disease and ANCA vasculitis

Maintenance therapy

Optimal duration of maintenance therapy:

- Optimal duration is between 18 months to 4 years after induction of remission.
- Longer duration of maintenance therapy may be considered for the following high relapse risk characteristics:
  - Anti-PR3 positive
  - GPA
  - History of prior relapse
  - Multiple and extensive organ involvement, particularly upper respiratory tract (ear, nose, throat)
  - Higher SCr

Choice of maintenance therapy

- First line: RTX alone or combination azathioprine (AZA) plus low-dose GC
- Other maintenance agents in nonsevere disease or if RTX cannot be used:
  - MMF maintenance is less effective in preventing relapse compared with AZA.
  - AZA and MTX are equally effective. MTX should not be used in patients with GFR less than 60 mL/min/1.73 m^2.

Suggestions for preferential selection of AZA plus low-dose GC versus RTX versus others are summarized in **Table 7.8**.

Table 7.8 Suggestions for preferential selection of AZA plus low-dose GC versus RTX versus others (KDIGO 2024)

Selection of azathioprine vs rituximab as maintenance therapy for ANCA-associated vasculitis

AZA plus low-dose GC may be preferred if:	Rituximab alone may be preferred if:
• Total IgG is <300 mg/dL. • Hepatitis B surface antigen is positive. • RTX availability is limited.	• PR3-ANCA disease • Relapse disease • AZA intolerance, eg, patients with thiopurine methyltransferase (TPMT) deficiency —The diagnosis may be made with measuring TPMT activity or genetic testing. • GC avoidance is important.
Other maintenance agents in nonsevere disease or if RTX cannot be used: • MMF maintenance is less effective in preventing relapse compared with AZA. • AZA and methotrexate have been shown to be equally effective.	

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; PR3, proteinase 3; RTX, rituximab.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int.* 2024;105(3S):S71-S116.

Therapeutic considerations for disease relapse

- RTX is preferred given higher remission rates, especially with PR3-ANCA.
- If CYC is used, do not reach cumulative dosages greater than 36 g due to increased malignancy risk.
- In non–life-threatening relapse, MMF may be considered, but the rate of relapse is increased. RTX is still preferred.

Therapeutic considerations for refractory disease

Refractory disease is defined as having no improvement by 4 weeks, improvement of less than 50% in 6 weeks of treatment as measured by the Birmingham Vasculitis Activity/Wegener granulomatosis score (BVAS/WG), or chronic persistent disease after more than 12 weeks.

- Increase GC dose.
- Add RTX to CYC or vice versa.
- Consider adding PLEX.
- Strategies to reduce infection risks: Avoid leukopenia, minimize GC dose, use high-dose IVIg with PLEX.

NOTE

- Discontinue IST in patients who still require dialysis support after 3 months and have no extrarenal manifestations.
- Disease monitoring: Modification of IST (ie, intensifying or reinitiating therapy) based on increasing ANCA titer alone is not recommended.
- Avoid overimmunosuppression, provide Pneumocystis carinii prophylaxis, and be vigilant with infectious complications in all patients receiving IST. Low-dose sulfamethoxazole/trimethoprim or alternative (eg, atovaquone) is advised for the duration of CYC course or for 6 months following RTX induction.

Natural history and prognosis

5-year renal and patient survival are approximately 65% to 75%.

Poor prognostic risks:

- Older age, higher presenting SCr or dialysis need at presentation, pulmonary hemorrhage
- MPO-ANCA patients tend to present with worse renal impairment and more chronic changes compared with those with PR3-ANCA. However, if MPO-ANCA is diagnosed early, it may be associated with better renal outcome compared with PR3-ANCA.
- Histopathologic sclerotic class is associated with poor kidney outcome, focal class does best. Discrepancies exist in kidney outcomes for crescentic and mixed classes.

- Persistent hematuria may suggest higher relapse rate.
- Recurrence of hematuria after complete resolution may suggest relapse.

Risks for higher relapse rates:

- Diagnosis of GPA
- ANCA: PR3-ANCA, ANCA positive at the end of induction or rise in ANCA titer
- Respiratory tract involvement (ear, nose, throat)
- More extensive disease
- Lower SCr
- History of relapse
- IST: lower CYC exposure, GC withdrawal

NOTE

The persistence of ANCA positivity, increase in ANCA titers, or change in ANCA negativity to positivity may be predictive of future disease relapse and should be considered when making treatment decisions.

Kidney transplantation

- Delaying transplantation until complete remission (CR) for 6 months or more is recommended.
- The persistence of ANCA positivity alone should not delay transplantation.
- Disease recurrence following transplant has been reported to be 0.02 to 0.03 per patient-year. This rate is not influenced by remission duration or ANCA status prior to transplantation.

LUPUS NEPHRITIS (LN)

Epidemiology

20% to 60% of patients with SLE will develop clinically significant LN.

Age

- Most patients who develop LN are younger than 55 years old.
- Severe nephritis is more common in children than older patients.

Gender differences

- Female-to-male predominance: 2:1 in prepubertal children → 4:1 in adolescents → 8 to 12:1 in adults → 2:1 in adults age greater than 60
- Males tend to have worse kidney outcomes compared with their female counterparts.

Race-related demographics

- SLE is more common in Hispanics and Blacks than Whites.
- Severe LN is more common in Blacks and Asians.

- Patients of African ancestry with APOL1 risk alleles are at increased risk for worse kidney outcomes.

Pathogenesis

The pathogenesis likely involves multiple components including genetic susceptibility, epigenetic phenomena, immunoregulatory dysfunction, hormonal imbalances, and various environmental factors. For interested readers, see **Appendix A7.2** for more detailed information regarding pathogenesis.

Diagnosis

Routine laboratory findings

Urine studies

Microscopic hematuria, acanthocytes, RBC or white blood cell casts, proteinuria with or without NS

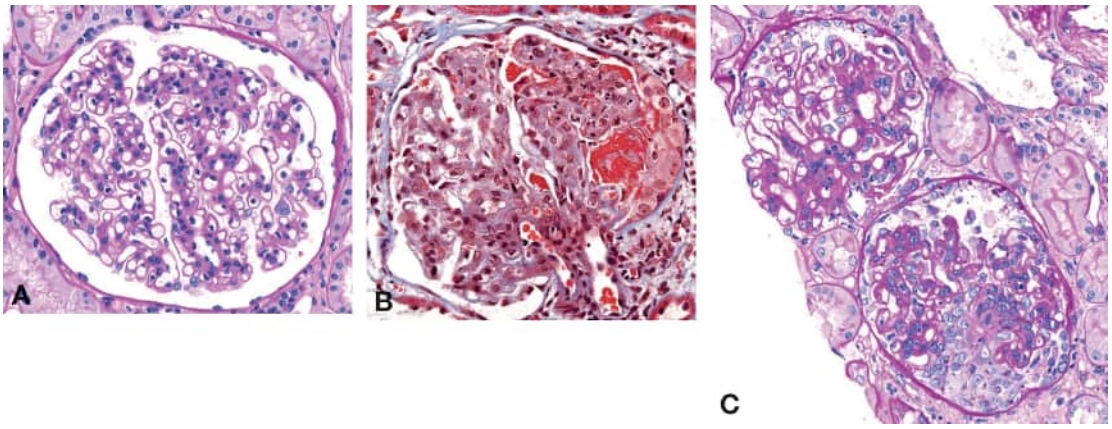
Serologies

- ANA: sensitive, not specific, for SLE
- Anti-Smith: specific for the diagnosis of SLE
- Anti-dsDNA, hypocomplementemia, and anti-C1q autoantibody levels are strongly associated with kidney involvement in patients with SLE and should be monitored in those at risk for LN or LN flare.

Kidney biopsy

- Performing a kidney biopsy is the gold standard for diagnosing LN.
- Kidney biopsy indications: active urinary sediment (eg, urine dipstick ≥2+ proteinuria at any level of specific gravity and spot uPCR ≥0.5 g/g Cr, ≥5% acanthocytes, RBC or white blood cell casts), 24-hour urine proteinuria 0.5 g or more, or unexplained rise in SCr

Histopathology (Figure 7.4)



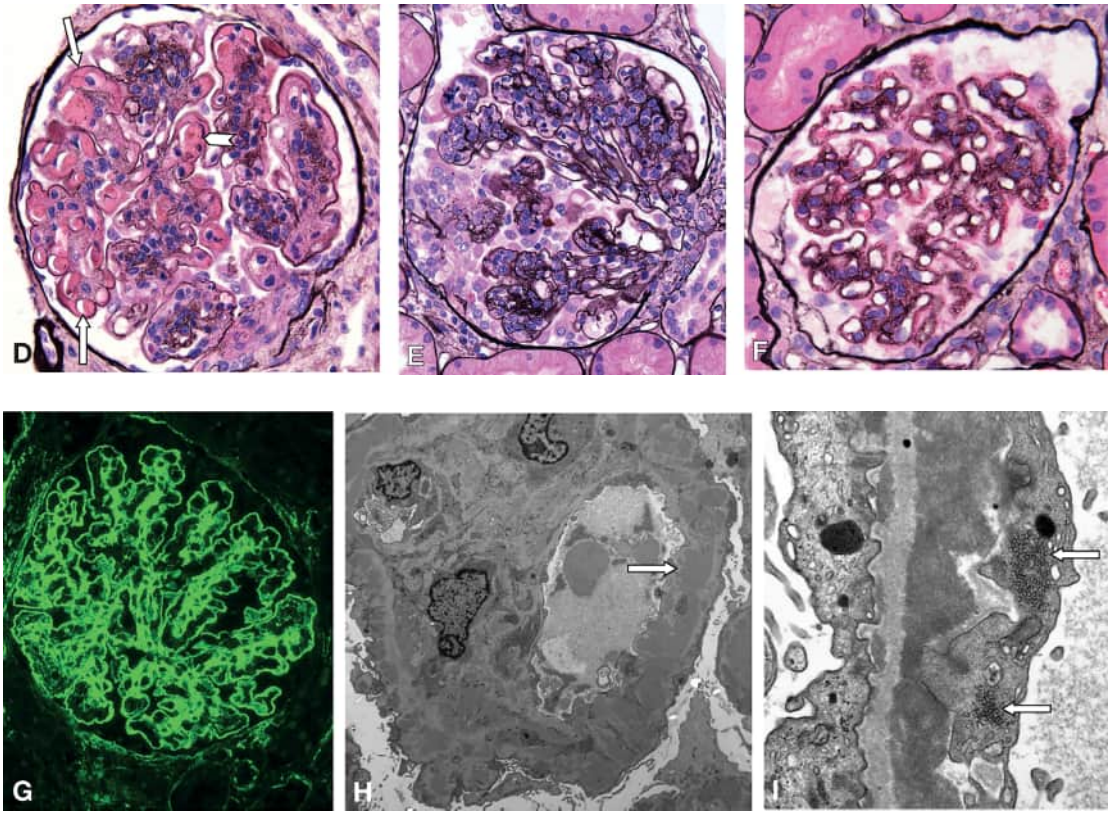


FIGURE 7.4 **Lupus nephritis.** A. Mesangial proliferative (Class II) (periodic acid-Schiff ×400). B. Segmental proliferation with leukocytes and a necrotizing/crescentic lesion (Masson trichrome ×400). C. Active focal lupus nephritis (Class III). There is segmental involvement of less than 50% glomeruli with active/proliferative features (endocapillary hypercellularity, cellular crescent). In chronic focal lupus nephritis, there is focal scarring/sclerosis (Periodic acid-Schiff ×200). D, E. Active diffuse lupus nephritis (Class IV). In (D), there are large subendothelial deposits forming wire loop lesions (arrows) and hyaline thrombi (arrowhead). In (E), there is more leukocytic infiltration with a segmental cellular crescent. F. Membranous lupus nephritis (Class V). Capillary walls are thickened with subepithelial deposits and spikes, with mild segmental mesangial hypercellularity (D-F. Jones silver ×200). G. Global mesangial and capillary wall staining for immunoglobulin G in mixed active diffuse and membranous lupus nephritis (classes IV + V) (×400). H. Electron microscopy showing large subendothelial (wire loop) (arrow), mesangial, and segmental subepithelial electron-dense deposits (×6,000). I. Tubuloreticular inclusions (arrows) in endothelial cell cytoplasm beneath subendothelial deposits. Small subepithelial deposits are also present (×29,000).

Classification of LN per the International Society of Nephrology/Renal Pathology Society:

LM:

Class I: minimal mesangial LN: normal glomeruli by LM; mesangial immune deposits by IF and EM only

Class II: mesangial proliferative LN: mesangial hypercellularity on LM; mesangial immune deposits by IF and EM

Class III: focal LN (<50% of glomeruli involved)

- Class III(A): active lesions (leukocytes, karyorrhexis, necrosis, cellular or fibrocellular crescents, large subendothelial deposits forming "wire loops" or "hyaline thrombi")
- Class III(A/C): active and chronic lesions

- Class III(C): chronic lesions (segmental or global glomerulosclerosis, fibrotic crescents)

Class IV: diffuse LN (≥50% glomeruli involved)

- Class IV(A): active lesions
- Class IV(A/C): active and chronic lesions
- Class IV(C): chronic lesions

Class V: membranous LN (>50% subepithelial deposits with or without mesangial hypercellularity); class V may occur with class III or class IV

Class VI: advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)

IF: "full house" staining for IgG (strong), IgA, IgM, C1q (strong), and C3. Location depends on the LN class.

EM: mesangial, subendothelial, and/or subepithelial depending on disease class

- Usually deposits in at least two glomerular locations
- Endothelial cell tubuloreticular inclusions are usually present.

Activity and chronicity indices: numerical scoring of weighted active and chronic features to determine potential response to therapy

- Active features (maximum score 24): glomerular necrosis, cellular/fibrocellular crescents, endocapillary hypercellularity, neutrophils/karyorrhexis, large subendothelial deposits (hyaline thrombi/wire loops), interstitial inflammation
- Chronic features (maximum score 12): global and segmental glomerulosclerosis, fibrotic crescents, tubular atrophy, interstitial fibrosis

Management (KDIGO 2024)

For all LN classes

Follow routine CKD management strategies and vaccinations as outlined in **Chapter 4: Chronic Kidney Disease**.

Antimalarials

- All patients with SLE including those with LN should be treated with an antimalarial (hydroxychloroquine (HC) 5 mg/kg/d or chloroquine dose 2.3 mg/kg/d or lower—lower dose may not achieve adequate blood levels to help reduce flares) unless contraindicated.
- Benefits of antimalarials: lower flare rates (including LN), higher response rates to therapy, slower progression of kidney disease, lower CVE and thrombotic events in patients with antiphospholipid antibodies (aPLs), improved lipid profile and bone mass preservation
- Caution with the use of antimalarials:
  - Increased risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, HC retinopathy in long-term users, accumulation in lysosomes causing the formation of multilamellar zebra bodies in podocytes mimicking Fabry disease (see "Fabry disease" section), cardiomyopathy, conduction abnormalities

- HC retinopathy risks: greater duration of use, concomitant tamoxifen use, eGFR less than 60 mL/min/1.73 m^2, HC dose greater than 5 mg/kg/d, use of chloroquine instead of HC
- Annual eye examination after 1 year of use in individuals with increased risk, otherwise after 5 years of use

Infections and vaccinations

- See "Management of complications common to glomerular/vascular diseases" section.
- Of note, there are anecdotal reports of new onset or flares of immune-mediated diseases following some vaccinations.

Considerations in counseling for contraception and pregnancy:

- Avoid estrogen-containing contraceptives in patients with aPLs.
- Use gonadotropin-releasing hormone analogs for fertility protection.
- Sperm and oocyte cryopreservation

Class I/II LN-specific therapy:

- Typically, class I/II LN presents with normal kidney function.
- Disease-specific therapy is not necessary.
- If patients present with nephrotic range proteinuria, evaluate for lupus podocytopathy similar to that seen with MCD or FSGS. Treatment with GC alone is generally adequate. Duration of treatment and maintenance have not been established. Maintenance with low-dose GC plus mycophenolic acid analogs (MPAA), AZA, or calcineurin inhibitor (CNI) is suggested, particularly in those with a history of relapse, is suggested.

Class III/IV LN-specific therapy

Table 7.9 summarizes recommended induction regimens and dosing for LN class III/IV. For dosing, see **Appendix A7.3**.

Table 7.9 Immunosuppressive regimens for lupus nephritis class III/IV (KDIGO 2024)

Glucocorticoids *plus* any of regimens below		Comments	Treatment duration

MPAA	–	• Dosing for MPAA:
		  • MMF 1.0-1.5 g bid or
		  • Mycophenolic acid sodium 0.72-1.08 g bid
			At least 6 mo

CYC	–	• Dosing for CYC:
		  • (Euro-Lupus): 500 mg IV q2wk × 6 doses, or
		  • NIH: 0.5-1.0 g/m^2 IV monthly × 6 mo, or
		  • Oral: 1.0-1.5 mg/kg/d po (max 150 mg/d) for 2-6 mo
		• Hematologic malignancy is associated with cumulative lifetime dose >36 g.
			Up to 6 mo

Triple therapy with belimumab + GC + (MPAA or reduced-dose CYC)			

Glucocorticoids *plus* any of regimens below		Comments	Treatment duration
• Dosing for belimumab: 10 mg/kg IV q2wk for 3 doses then q4wk • Kidney benefit was most marked in patients with baseline uPCR <3 g/g. • FDA approved both intravenous and subcutaneous formulations; higher trough level is achieved with subcutaneous administration.			
Belimumab +	MPAA	• There is moderate evidence that adding belimumab is better than GC + MPAA alone.	Belimumab may be used up to 2.5 y in terms of safety.
Belimumab +	Reduced-dose CYC	• Dosing for IV CYC: 500 mg IV q2wk × 6 doses (total 12 wk) • There is moderate evidence that adding belimumab is better than GC + CYC alone.	
Triple therapy with CNI + GC + MPAA			
• CNI may be particularly useful in patients with high-grade proteinuria associated with extensive podocytopathy, nephrotic range proteinuria. • May consider CNI when kidney function is not severely impaired (ie, eGFR ≤45 mL/min/1.73 m^2) • There is no data on voclosporin + CYC combination therapy at the time of this writing.			
MPAA +	CNI: voclosporin	• Dosing for voclosporin: 23.7 mg bid • There is high-certainty evidence that adding voclosporin to standard GC + MPAA is better than GC + MPAA alone.	CNI up to 3 y as long as eGFR >45 mL/min/1.73 m^2
MPAA +	CNI: tacrolimus	• Tacrolimus (trough level ~5.5 [4-7] ng/mL) • Reduce MPAA dose in patients on tacrolimus with SCr <3.0 mg/dL. • Data mainly from Chinese patients	
MPAA +	CNI: cyclosporine	• Cyclosporine (maintenance trough level ~50-100 ng/mL) • Consider cyclosporine when voclosporin and tacrolimus are not available.	

Abbreviations: CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GC, glucocorticoid; KDIGO, Kidney Disease: Improving Global Outcomes; max, maximum; MMF, mycophenolate mofetil; MPAA, mycophenolic acid analog; uPCR, urine protein-to-creatinine ratio.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 clinical practice guideline for the management of lupus nephritis. *Kidney Int.* 2024;105(1S):S1-S69.

Induction therapy: GCs plus any one of the following:

- MPAA, *or*
- Low-dose IV CYC, *or*
- Belimumab *and either*
  - MPAA *or*
  - low-dose IV CYC, *or*
- MPAA plus any CNI

    - CNI options: voclosporin, tacrolimus (data mainly from Chinese patients), or cyclosporine (use cyclosporine if voclosporin and tacrolimus are not available)
    - Consider MPAA plus CNI regimen when kidney function is not severely impaired (ie, eGFR ≤45 mL/min/1.73 m^2).
- Alternative options: GC plus either AZA or leflunomide if none of the above induction regimens is feasible or tolerable. However, these alternative options may be associated with inferior efficacy, increased rate of disease flares, and/or drug toxicities.

Notes regarding induction therapy:

- GCs
    - IV methylprednisolone pulse at the start of active LN therapy has not been well studied but commonly used at 500 mg/d (range 250-1,000 mg/d) up to 3 daily doses. IV pulse is generally given in patients who present with a clinical syndrome of RPGN, acute and severe deterioration of kidney function often accompanied by a high proportion of crescents or vascular lesions on kidney biopsy, or when there are severe extrarenal manifestations (eg, central nervous system [CNS] or lung involvement).
    - Reduced-dose prednisone (as low as 0.5-0.7 mg/kg/d) following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN.
    - Higher oral dose of prednisone (eg, 0.8-1.0 mg/kg/d) may be used if no IV methylprednisolone is used.
    - Prednisone taper is generally down to 2.5 to 5.0 mg/d by week 20.
- MPAA:
    - Higher response rates for MMF compared with CYC in Hispanic patients, 60.9% versus 32%, $P = .011$ (ALMS study)
    - Higher dose of MMF (eg, 3 g/d instead of 2 g/d) did not result in greater efficacy in non-Black patients from kidney transplant clinical trials. Adverse effects may be associated with the greater dose.
- CYC-containing regimen:
    - IV CYC can be used as initial therapy for active class III/IV LN in patients who have difficulty adhering to an oral regimen.
    - Oral versus IV CYC: equivalent efficacy
    - Adverse events: bladder toxicity, hematologic malignancy related to total lifetime exposure greater than 36 g, myelofibrosis (>80 g), ovarian failure (>7.5-15 g/m^2 for young to older pediatric patients, 300 mg/kg for adults)
    - Renal dose: 20% and 30% reduction for creatinine clearance (CrCl) 25 to 50 and 10 to 25 mL/min, respectively
    - Adjust CYC dose to keep nadir leukocyte count 3,000/μL or higher (10-14 days for IV CYC and 1 week for po CYC).
    - Use sodium-2-mercaptoethane (mesna) to minimize bladder toxicity.
    - Fertility protection while on CYC treatment:
        - Women: leuprolide, ovarian tissue cryopreservation

        - Men: testosterone (efficacy poorly established), sperm banking
- Belimumab-containing regimen:
    - Kidney benefit was most marked in patients with baseline uPCR less than 3 g/g Cr. Whether higher proteinuria affects belimumab clearance remains to be elucidated.
    - Patients identified as Black race appeared to have lower treatment response compared with other racial groups, but with greater response compared with placebo.
    - There is moderate evidence that adding belimumab to GC plus reduced-dose CYC or GC plus MPAA dual therapy provides better renal response rates with similar incidence of adverse events.
- CNI-containing regimen:
    - "There is high-certainty evidence showing that triple therapy with voclosporin, standard-dose MPAA, and rapid-tapering GC is superior to MPAA and rapid-tapering GC in achieving renal response with similar incidence of adverse events" (KDIGO 2024).
    - May be particularly useful in patients with high-grade proteinuria associated with extensive podocytopathy. In addition to reducing interleukin-2 (IL-2) transcription and T-lymphocyte proliferation, CNIs also have a direct modulatory effect on podocyte cytoskeleton.
    - May be considered in patients who cannot tolerate standard-dose MPAA or cannot or refuse CYC-based regimen
    - There is currently no data on voclosporin plus CYC therapy.
- RTX may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.

Maintenance therapy:

- MPAA (MMF 1-2 g/d or mycophenolic acid 720-1,440 mg/d) is the first choice because it decreases the risk of LN relapse compared to AZA.
- AZA (1.5-2.0 mg/kg/d) is an alternative to MPAA.
- If both MPAA and AZA cannot be used, consider:
    - CNI: tacrolimus (level ~4-6 ng/mL) or cyclosporine (level 50-100 ng/mL), or
    - Mizoribine (~3-5 mg/kg/d) or leflunomide (~10-20 mg/d)
- For patients who received triple immunosuppression as initial therapy for active LN, continue with the triple immunosuppression as maintenance.
- Maintenance therapy should be continued for a minimum total treatment duration of 36 months (induction + maintenance). Note that despite 36 months or more of immunosuppression and 12 months or more of sustained complete clinical renal response, up to 50% of patients may still have inflammatory histologic activity on repeat kidney biopsy and associated increased risk for LN flares. Repeat kidney biopsy may be considered to determine appropriateness of withdrawal of maintenance therapy.
- GCs: Discontinuation of GC can be considered after patients have maintained a complete clinical renal response for 12 months or more.

Class V LN-specific therapy

- Class V LN does not usually remit spontaneously as does primary MN.
- Disease progression is associated with the degree of proteinuria.

For subnephrotic proteinuria: Initiate immunosuppression based on extrarenal indications.

For nephrotic range proteinuria:

- GC plus MMF is a "reasonable first choice."
- CYC may be considered for 6 months or less if MMF is ineffective.
- Other agents to consider: CNI, RTX, AZA

Management considerations for poor response to the treatment of LN

- Consider repeat biopsy to assess chronicity or other diagnoses (eg, thrombotic microangiopathy [TMA]).
- Consider additional therapeutic options if truly refractory to first-line treatment regimens:
  - Add RTX or other biologic therapies.
  - Use extended course of IV pulse CYC.
  - Enroll in clinical trials if possible.

Relapse LN

Provide the same initial therapy used to achieve the original response with considerations for alternative therapy in those who already received high cumulative dose of CYC.

Poor prognostic indicators

- Patient characteristics: African or Hispanic ancestry, male gender, pediatric onset, frequent relapses, incomplete remission, neuropsychiatric lupus, proteinuria greater than 4 g/d at diagnosis
- Serologies: antiphospholipid syndrome (APS) or presence of aPLs, persistent hypocomplementemia, elevated anti-dsDNA or anti-C1q antibodies
- Histologic findings: crescentic GN, TMA, or extensive tubulointerstitial fibrosis
- A change from normal to abnormal SLE serologies (eg, hypocomplementemia or increase in anti-dsDNA antibody titers) may suggest an impending flare.

Lupus and Pregnancy

Measurable SLE disease activity is present in 40% to 50% of pregnancies, with LN occurring in up to 75% of these cases.

Active SLE during pregnancy is associated with:

- Increased risk of preeclampsia to 30% compared to 5% in the general population
- Increased risk of fetal death and preterm birth

Active LN during pregnancy is associated with:

- Increased maternal adverse outcomes including increased risk of gestational HTN, preeclampsia, and maternal death. There is evidence to suggest that LN classes III/IV may be associated with greater risk for HTN/preeclampsia compared to other LN classes.
- Likely increased risks of preterm birth, intrauterine growth restriction, stillbirth, and neonatal death (inconsistent findings in the literature)

Risk factors for adverse outcomes in pregnancy:

- Active disease at conception
- Positive aPLs
- HTN, proteinuria, reduced GFR in the first trimester

Management of SLE/LN in pregnancy:

Pregnancy planning

- Delay pregnancy for at least 6 months after complete remission.
- Medication contraindications/not recommended during pregnancy:
  - Use of CYC, MMF, ACEi/ARB is not recommended due to potential teratogenicity. Patients who become pregnant while being treated with MMF may be switched to AZA.
  - MTX is teratogenic and should be discontinued 3 months or more prior to conception.
  - Leflunomide is contraindicated in pregnancy and should be discontinued for 2 years or more before trying to conceive.

Intrapregnancy considerations:

- HC maintenance therapy should be continued during pregnancy. Discontinuation of HC may lead to lupus flares including LN.
- Start low-dose aspirin 100 mg/d or lower at conception or as soon as pregnancy is recognized to reduce the risk of preeclampsia, intrauterine growth retardation, and fetal loss.
- LN relapse during pregnancy should be treated with GC, and if necessary, AZA.

Postpartum considerations:

- GC or AZA given during pregnancy should not be tapered until at least 3 months postpartum.
- Medication considerations with breastfeeding:
  - MPAA is contraindicated in patients who breastfeed.
  - HC, tacrolimus, low-dose AZA, and prednisone are considered safe.

Differentiating between lupus flare and preeclampsia in a woman with AKI:

- Lupus flare: AKI may occur at any time including prior to 20 weeks of gestation and postpartum, presence of hypocomplementemia, RBC casts, and leukopenia.

- Preeclampsia: AKI only occurs after 20 weeks of gestation with the absence of findings seen with lupus flare (eg, hypocomplementemia, increased anti-dsDNA titer).

ANTI-GBM DISEASE (GOODPASTURE SYNDROME)

Epidemiology

- Incidence: 0.5 to 1.0/million/y
- Predominantly Caucasians, recognized in Asians, rare in other ethnicities
- Peak age 20 to 30 years with slight male predominance, more often presenting with pulmonary hemorrhage
- Smaller peak at age 60 to 70 years with female predominance, more likely to have isolated GN
- Genetic predisposition: HLA-DR15

Pathogenesis

- Typically, anti-GBM disease is caused by autoantibody formation against the noncollagenous (NC1) domain of type IV collagen α3 chain, α3(IV)NC1, a.k.a. the "Goodpasture antigen" present on the GBM. Anti-GBM disease may also be caused by autoantibody formation against other GBM constituents (eg, α3-α5(IV) collagen chains).
- Type IV collagen chains are also present in alveoli, cochlea, corneal basement membrane and Bruch membrane, choroid plexus, and some endocrine organs. Presenting symptoms may be related to injury of these organs.
- Exposed/injured basement membrane seen with environmental insults on alveolar membrane (eg, cocaine inhalation, infections, smoking, pulmonary edema, or exposure to metal dust, organic solvents, or hydrocarbons) and/or GBM injury with extracorporeal shock wave lithotripsy impose risks for anti-GBM disease.

Clinical Manifestations

- Disease develops over weeks to months.
- Hemoptysis of varying degrees, incidental microscopic hematuria with disease progressing over months to years or acute GN, edema, HTN
- Chest radiograph: patchy parenchymal opacifications, typically bilateral and bibasilar, and sparing apices and costophrenic angles

Histopathology (Figure 7.5)

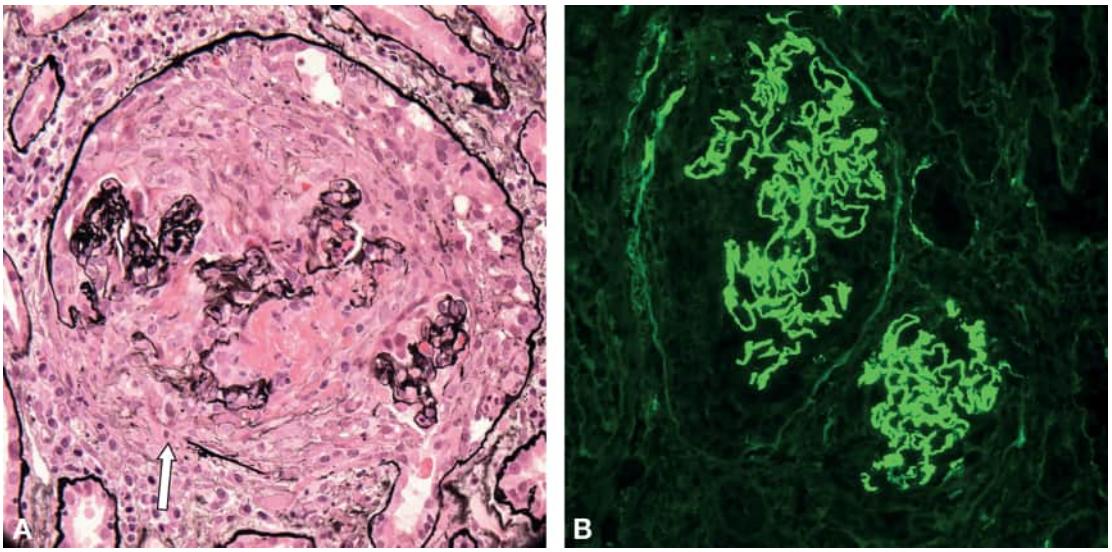


FIGURE 7.5 **Anti-glomerular basement membrane antibody nephritis.** A. Cellular crescent causing destruction of Bowman capsule segmentally (arrow) (Jones silver ×400). B. Linear capillary wall staining for immunoglobulin G (×200).

LM: glomerular crescents without mesangial hypercellularity. Crescents are in the same stage (all cellular, fibrocellular, or fibrotic) due to "one-shot" anti-GBM antibody production.
IF: glomerular capillary wall IgG in a linear pattern (Note that some patients with Alport syndrome may present with a similar pattern after kidney transplantation. See Alport syndrome.)
EM: no deposits
Management (**Appendix A7.4** summarizes management of anti-GBM with drug dosing.)

Immunosuppressive therapy

- KDIGO recommends prompt initiation of CYC and GC plus PLEX in all patients with anti-GBM GN.
- Exception to IST initiation: patients who are dialysis dependent at presentation or who have 100% crescents or more than 50% global glomerulosclerosis in an adequate biopsy sample *and* do not have pulmonary hemorrhage

GC should be started within 24 hours prior to tissue diagnosis if high clinical suspicion due to rapidly progressive disease. Upon diagnosis confirmation, add CYC and PLEX.
CYC should be given for 2 to 3 months and GC for about 6 months. If anti-GBM antibodies persist after 3 months of CYC, continuation of treatment with either AZA or MMF in combination with GC is suggested.

Plasmapheresis should be performed until anti-GBM antibodies become undetectable (typically in 2-3 weeks). PLEX should be done with fresh frozen plasma (FFP) in patients with alveolar hemorrhage or immediately following kidney biopsy. If albumin is used, administer FFP at the end of PLEX. Replace fibrinogen with cryoprecipitate as needed.

Maintenance IST for anti-GBM GN is not necessary.

- Relapses are uncommon (0%-6% of cases).
- Relapses may be associated with continuing smoking or exposure to lung irritants. Treatment of patients without detectable anti-GBM antibodies beyond 6 months is not recommended. Advise smoking cessation whenever applicable.

Special treatment consideration for coexistence of anti-GBM and ANCA

Patients with GN who are both anti-GBM and ANCA positive should be treated with maintenance therapy as for patients with AAV. Double-positive patients may have a better chance of kidney recovery from dialysis dependence than those with only anti-GBM disease.

Refractory disease (rare, <10% of cases)

- Consider RTX trial.
- In case of intolerance to CYC or reluctance to use CYC, consider MMF.
- Other potential therapeutic options:
  - Imlifidase is an IgG-degrading endopeptidase from *Streptococcus pyogenes* that cleaves human IgG into F(ab)2 and Fc fragments, thereby inhibiting antibody- and complement-dependent cytotoxicity. The use of imlifidase was associated with better renal outcome compared with historical data in a phase 2a trial. At 6-month follow-up, 67% (10/15 patients) were dialysis independent compared with 18% (9/50) in a historical control cohort. More safety data and confirmatory studies are warranted.
  - Immune adsorption therapy to remove anti-GBM antibodies

Prognosis and Prognostic Indicators

- Higher presenting SCr and higher percentage of crescents portend worse prognosis. Renal recovery is rare if presenting SCr is greater than 6 mg/dL.
- With rapid and aggressive therapies, 5-year survival rate exceeds 90%, 5-year kidney survival rate of 25% to 50%, and less than 30% require long-term kidney replacement therapy.

Kidney Transplantation

- Defer transplantation until anti-GBM antibodies are undetectable for at least 6 months.
- Recurrent disease is unusual presumably due to the use of IST for the allograft kidney, unless transplant is done while anti-GBM antibodies are detectable.
- New-onset anti-GBM disease following kidney transplantation should raise the suspicion of Alport syndrome in the native kidneys.

GLOMERULAR INJURY ASSOCIATED WITH INFECTIONS

Clinical/Morphologic Entities of Bacterial Infection–Related GN Include:

- PIGN, poststreptococcal GN (PSGN)
- Shunt nephritis
- Infective endocarditis-related GN
- IgA-dominant infection-related GN (IgADIRGN)

Notable Laboratory Findings for Bacterial Infection–Related GN:

- Urinalysis with glomerular hematuria (dysmorphic RBCs), white blood cells, proteinuria, with or without AKI
- Hypocomplementemia (C3, C4), elevated rheumatoid factor, cryoglobulin, and anti–factor B antibody levels may be seen. Anti-complement factor B (CFB), which activates the alternative complement pathway, is more commonly seen in acute PIGN than in C3 glomerulopathy.
- ANCA (anti–PR3-ANCA) may be seen with shunt nephritis and endocarditis.

Management Common to All Bacterial Infection–Related GN:

- Treat associated edema, HTN, and proteinuria per routine for any patient with GN/CKD.
- Provide antibiotics for any ongoing active infections per culture sensitivity and local guidelines. Note that antibiotic therapy does not alter the GN course in PIGN.
- The benefit of using GC and IST is unproven and may be associated with serious adverse effects in all forms of bacterial infection–related GN.

Postinfectious Glomerulonephritis

PIGN has replaced PSGN because streptococcal infections account for only 28% to 47% of PIGN. *Staphylococcus aureus* or *Staphylococcus epidermidis* account for 12% to 24% of cases and gram-negative bacteria up to 22%.

Epidemiology

- The incidence of PIGN has greatly decreased in industrialized countries.
- Traditionally, a disease of children, PIGN is now seen in debilitated older patients with chronic alcoholism, DM, IV drug abuse, and poor communities due to the lack of early medical care, antibiotics, and/or fluorinated water. Fluorinated water reduces expression of virulence factors in *S. pyogenes*.

Pathogenesis

- Nephritogenic bacterial antigens induce an immune response that leads to glomerular damage.
- Putative nephritogenic streptococcal antigens include glyceraldehyde-3-phosphate dehydrogenase (GAPDH), streptococcal pyrogenic exotoxin B (SPEB) and its more immunogenic precursor zymogen. Incubation is approximately 2 weeks after throat infection versus several weeks post skin infection.

Clinical manifestations

- Common presentation: HTN, edema, hematuria "coca cola urine." Azotemia is common in adults, and less commonly, NS.
- May occur 1 to 2 weeks following pharyngitis or 4 to 6 weeks following impetigo

Laboratory findings for PIGN

- C3 is low in more than 90%; C4 is typically normal; serum IgG and IgM are elevated in 80%.
- Cryoglobulins and rheumatoid factor are elevated in up to one-third of cases.
- Anti-DNA and ANCA may be positive in rare cases.

Laboratory findings specific for PSGN

- Positive *Streptococcus* culture in up to 70% during epidemics; 20% to 25% of sporadic cases
- Antistreptolysin O (ASO) titers are increased in greater than two-thirds with PSGN post throat infection.
- Anti-DNAse B titers are increased in 73% of post impetigo cases (>2 times normal).
- Others: Streptozyme panel (ASO, anti-DNAse B, antihyaluronidase, antistreptokinase) is more sensitive and is positive in more than 80%.

Diagnosis

- Kidney biopsy is not required to diagnose PIGN, especially during epidemics. Diagnosis is often made based on history, physical findings, and laboratory data.
- Kidney biopsy may be indicated when the clinical presentation is atypical or hypocomplementemia persists beyond 3 months.

Histopathology (Figure 7.6)

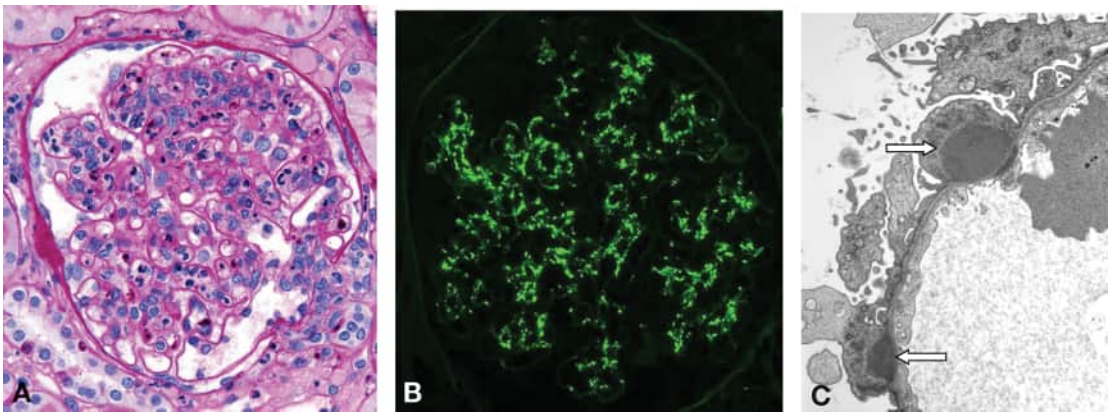


FIGURE 7.6 **Postinfectious (infection-related) glomerulonephritis.** A. Global endocapillary hypercellularity with many leukocytes, including neutrophils, occluding glomerular capillary lumens (periodic acid-Schiff ×400). B. Irregular granular C3 in glomerulus (×400). C. Individual "hump"-shaped subepithelial deposits (arrows) (×19,000).

LM: leukocytes, often neutrophils, in and occluding glomerular capillaries (large "bloodless" glomeruli). Crescents may be present.

IF: irregular granular capillary and mesangial strong staining for C3 usually with small amounts of IgG and/or IgM, described as "starry sky," "garland," and "mesangial" patterns
EM: large single subepithelial "hump" or "gumdrop" shaped deposits often at the mesangial waist or notch area where the capillary meets the mesangium

Natural history/prognosis

- Prognosis is excellent in children. PIGN typically resolves within a few weeks.
- Prognosis is worse in adults. Acute azotemia may be seen in 60% to 70%, congestive heart failure in 40%, and early mortality up to 20% to 25%. Some adults may have persistently low GFR.
- Mild proteinuria less than 500 mg/d may persist for several months.
- Microscopic hematuria may persist up to a year.

Management

In addition to treating any ongoing infections, preventive antimicrobial therapy may be considered for at-risk population and household members during epidemics.

NOTE

In PIGN, hypocomplementemia typically normalizes within 3 months. If hypocomplementemia persists, consider other glomerular diseases such as LN or C3 glomerulonephritis (C3GN).

Shunt Nephritis

Shunt nephritis may occur from months to many years after insertion. This entity is becoming rare because of earlier recognition and treatment of infection.

Pathogenesis

- Shunt nephritis is an IC-mediated GN that may develop as a complication of chronic infection of ventriculoatrial, ventriculojugular, or ventriculoperitoneal shunts.
- Typical organisms include *Staphylococcus epidermidis, S. albus, or S. aureus.*

Clinical manifestations

- Microscopic hematuria and proteinuria (often nephrotic range), occasional elevated SCr, HTN, prolonged fevers, or signs of chronic infection in a patient with an implanted shunt
- ANCA titer may be positive.

Histopathology

LM: usually a membranoproliferative glomerulonephritis (MPGN) pattern of injury
IF: granular deposits of IgG, IgM, and C3
EM: electron-dense mesangial and subendothelial deposits

Management

In addition to providing appropriate antibiotics, remove infected shunts as appropriate.

Infective Endocarditis-Related GN

- Infective endocarditis-related GN may be seen in the older patients even without underlying heart disease and in patients with IV drug usage, HIV, hepatitis C, diabetes, prosthetic heart valves, and/or structural heart disease.
- *S. aureus* has replaced *Streptococcus viridans* as the leading cause, with the highest risk in IV drug users.

Clinical manifestations

- Patients may present with AKI (79%), acute nephritis (9%), RPGN (6%), and NS (6%).
- Hypocomplementemia: low C3 in approximately 50%, low C4 in approximately 20% of cases
- ANCA and ANA are present in approximately 20% to 30%.

Histopathology

LM: crescentic GN in more than 50% of the patients, with fewer showing diffuse proliferative GN and mesangial proliferative GN
IF: Glomeruli show C3 dominance with IgG in about 25% and IgA in up to 50% of those with staphylococcal infections.

- IgG is present in only 15% of those with crescents.
- C3 predominance without C1q or C4 suggests alternative rather than classic complement pathway activation.

EM: mesangial and capillary wall deposits; subepithelial "hump" deposits are rare.

IgA-Dominant Infection-Related GN

Clinical manifestations/diagnosis

- Acute GN with declining kidney function, microscopic or gross hematuria, and either nephrotic or nephritic proteinuria in the presence of active blood or tissue infection
- Risk factors: DM, HTN, heart disease, malignancy, alcohol or substance abuse, kidney transplantation
- Laboratory findings: low complement C3, C4 less often than PIGN; serum IgA may be elevated.

Histopathology

LM: Biopsy often shows endocapillary hypercellularity with prominent neutrophil infiltration; A minority of cases may have isolated mesangial proliferative or infrequently crescentic GN.

IF: dominant IgA or co-dominant IgA and C3 mesangial and capillary wall staining, often with κ LC equal to or exceeding λ. May be weaker staining for IgG or IgM
EM: mesangial and capillary wall electron-dense deposits, the latter often with subepithelial "humps" and less frequent subendothelial locations. Cryoglobulins, when present, often lack the usual substructure.

Prognosis

- Kidney function recovery is possible with treatment of infection, but less than 20% return to baseline.
- Dialysis support may be needed during AKI.

Ig- and Complement-Mediated MPGN Pattern of Injury

Background

- MPGN pattern of injury is characterized by lobular accentuation of the tufts and capillary wall double contours.
- MPGN is categorized based on IF microscopy findings:
  - IC deposits (with or without complement deposition),
  - Dominant complement deposits, or
  - Neither IC nor complement deposits
- IF microscopy categorization above helps narrow down the differential diagnosis for the underlying MPGN etiology (**Figure 7.7**).

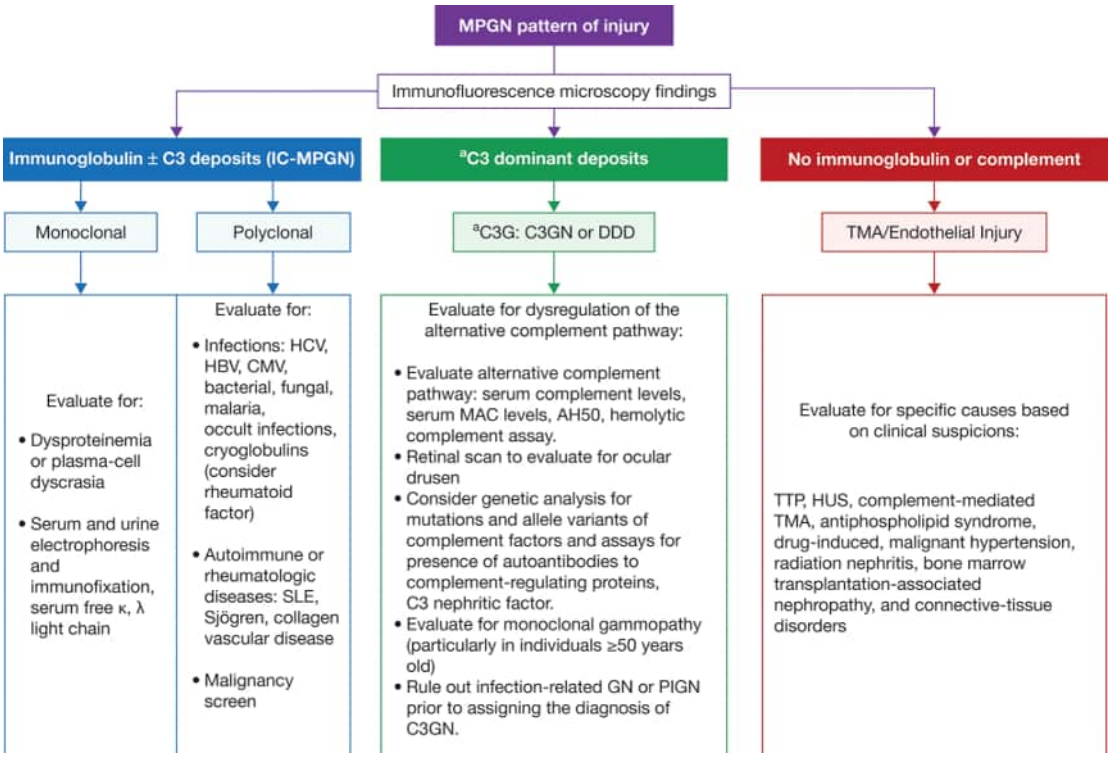
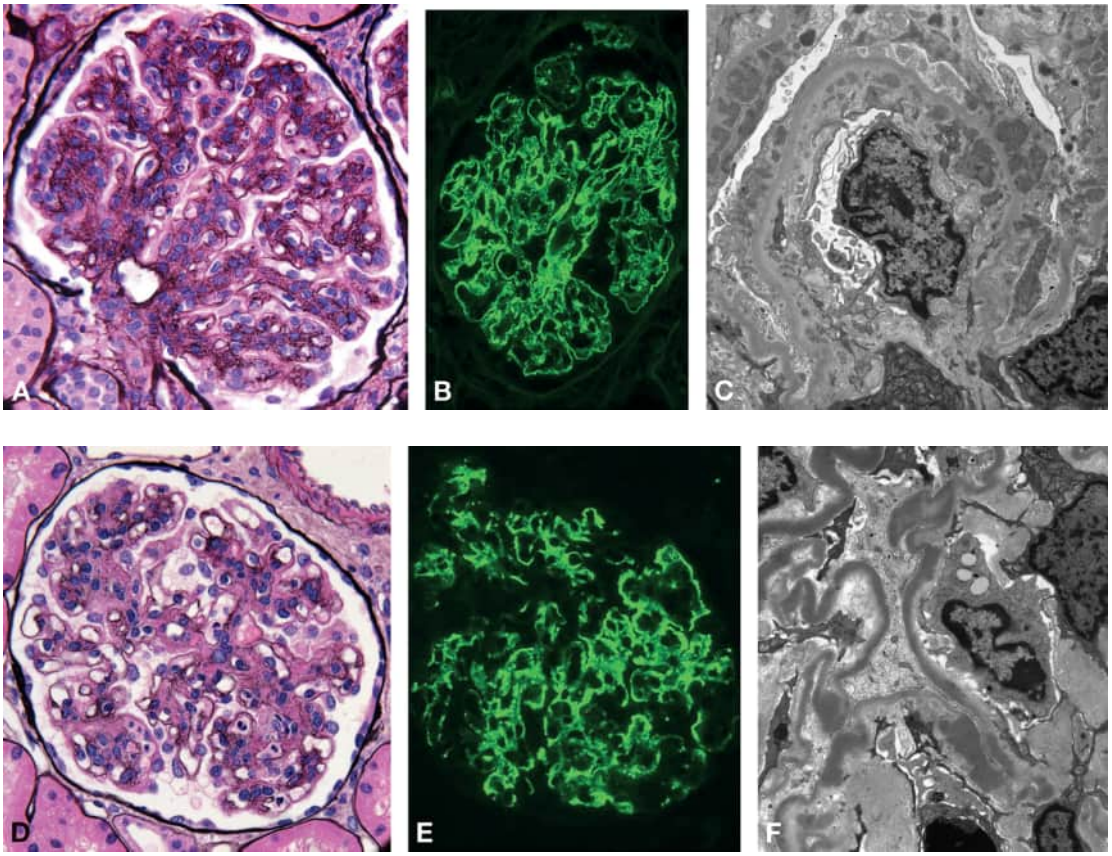

MPGN pattern of injury
Immunofluorescence microscopy findings
Immunoglobulin ± C3 deposits (IC-MPGN)
[a]C3 dominant deposits
No immunoglobulin or complement
Monoclonal
Polyclonal
[a]C3G: C3GN or DDD
TMA/Endothelial Injury
Evaluate for:
• Dysproteinemia or plasma-cell dyscrasia
• Serum and urine electrophoresis and immunofixation, serum free κ, λ light chain
Evaluate for:
• Infections: HCV, HBV, CMV, bacterial, fungal, malaria, occult infections, cryoglobulins (consider rheumatoid factor)
• Autoimmune or rheumatologic diseases: SLE, Sjögren, collagen vascular disease
• Malignancy screen
Evaluate for dysregulation of the alternative complement pathway:
• Evaluate alternative complement pathway: serum complement levels, serum MAC levels, AH50, hemolytic complement assay.
• Retinal scan to evaluate for ocular drusen
• Consider genetic analysis for mutations and allele variants of complement factors and assays for presence of autoantibodies to complement-regulating proteins, C3 nephritic factor.
• Evaluate for monoclonal gammopathy (particularly in individuals ≥50 years old)
• Rule out infection-related GN or PIGN prior to assigning the diagnosis of C3GN.
Evaluate for specific causes based on clinical suspicions:
TTP, HUS, complement-mediated TMA, antiphospholipid syndrome, drug-induced, malignant hypertension, radiation nephritis, bone marrow transplantation-associated nephropathy, and connective-tissue disorders

FIGURE 7.7 Classification of membranoproliferative glomerulopathy (MPGN) based on findings of immunofluorescence microscopy.

Abbreviations: AH50, alternative complement pathway assay; CMV, cytomegalovirus; DDD, dense deposit disease; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HUS, hemolytic-uremic syndrome; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis; MAC, membrane-attack complex; PIGN, postinfectious glomerulonephritis; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

[a]Complement-mediated MPGN: There may also be dominant C4 deposits, in which case the lesion would be C4G: C4GN or DDD.

Histopathology (Figure 7.8):



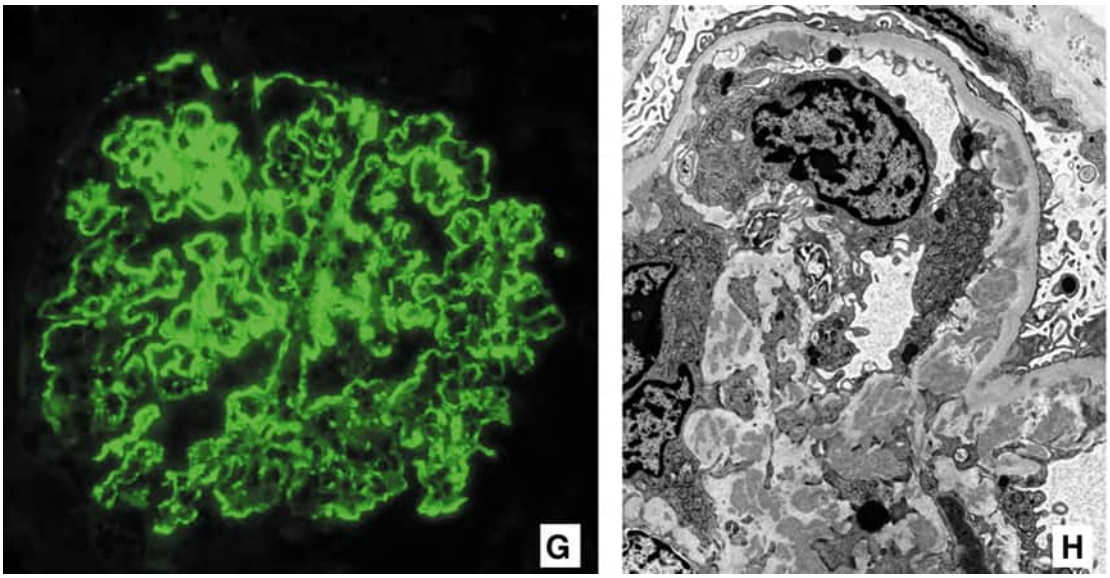


FIGURE 7.8 Membranoproliferative glomerulonephritis (MPGN) pattern of injury. A. Lobular hypercellular glomerulus (Jones silver ×400). B. Immunoglobulin G in a peripheral granular and mesangial pattern in immune complex–mediated MPGN (×250). C. Subendothelial deposits with new subendothelial basement membrane deposition forming a double contour in immune complex–mediated MPGN. There also are scattered subepithelial deposits (×10,000). D. Silver-negative material in widened mesangial regions and capillary walls. This may be seen with dense deposit disease or C3 glomerulonephritis (Jones silver ×400). E. Coarse linear and segmental coarse granular C3 deposition in dense deposit disease (×400). F. Electron-dense transformation of capillary basement membranes and segmentally in mesangial matrix in dense deposit disease (×10,000). G. Granular to confluent granular mesangial and segmental capillary wall staining for C3 (×400). H. Electron-dense deposits in subendothelial and mesangial locations in C3 glomerulonephritis (×10,000).

LM: lobular appearance of the tufts with mesangial and endocapillary hypercellularity, and capillary wall double contours. There may or may not be crescents.
IF: may show capillary wall and mesangial sole or dominant C3 (C3Gs), C3 with other Igs and C1q or C4 (immune complex–mediated MPGN [IC-MPGN]), or negative staining (endothelial cell injury) depending on the underlying pathogenesis
EM: When the IF is positive, there may be subendothelial deposits with mesangial migration and interposition with duplication of basement membrane forming capillary double contours. There are variable mesangial, subepithelial, and/or intramembranous deposits depending on the disease process.

Pathogenesis

Immune complex–mediated MPGN (IC-MPGN):

- IF microscopy shows Ig and/or complement deposits.
- Proposed pathogenesis:
  - Inciting event: There is a chronic increase in Ig production due to infections, autoimmune disease, malignancies, or monoclonal gammopathies.
  - Activation of classic complement pathway: Binding of Igs to GBM activates the complement cascade and induces cellular proliferative inflammatory changes.
  - Reparative phase: Mesangial cells extend along the subendothelial area, and, along with endothelial cells, produce new subendothelial GBM, forming capillary wall "tram

tracks or double contours." The new GBM may entrap subendothelial capillary wall deposits, mesangial cell cytoplasm with or without inflammatory cells.

- Conditions leading to increased Ig production, thus IC-MPGN:
  - Infections: chronic viral infections (hepatitis C > hepatitis B with or without cryoglobulins); bacterial infections (endocarditis, shunt/indwelling catheter nephritis, abscesses; common organisms: *Staphylococcus, Mycobacterium tuberculosis, streptococci, Propionibacterium acnes, Mycoplasma pneumoniae, Brucella, Coxiella burnetii, Nocardia, meningococcus*), fungal infections, parasitic infections
  - Autoimmune: SLE, Sjögren, rheumatoid arthritis, mixed connective tissue disease
  - Malignancies: lymphomas, chronic lymphocytic leukemia (CLL), carcinomas
  - Paraproteinemias: multiple myeloma (MM), Waldenström macroglobulinemia, or indolent clonal plasma cell, or lymphocytic disorder with or without cryoglobulins
    - Direct deposition of monoclonal Ig causing kidney injury (eg, immunotactoid glomerulopathy, cryoglobulinemic GN, proliferative GN with monoclonal Ig deposits [PGNMID])
    - Detection of a paraprotein in the deposits may require an antigen-retrieval technique on the LM specimen followed by routine IF.

Complement-mediated MPGN (C3- or C4-dominant deposits), C3-dominant glomerulopathy (C3G) or C4G:

- IF shows dominant C3 (or C4) deposits, where "dominant" is defined as having C3 (or C4) deposition at least two orders of magnitude greater than that of any other immune reactants.
- Pathogenesis involves alternative complement pathway dysregulation.
  - Dysregulated complement activation leads to abnormal C3 convertase activity and resultant inflammatory changes, endothelial/GBM/podocyte injury, and subsequent reparative phase similar to that seen with IC-mediated injury.
  - Dysregulation of complement activation may occur *via* different mechanisms:
    - Antibody formation against factor H, factor B, and nephritic factors (C3, C4, C5). C3 nephritic factor binds to and stabilizes C3 convertase, thereby prolonging its half-life and allowing continuing activation of the alternative pathway.
    - Mutations/genetic variants of complement regulators: CFH, CHI, CFB, C3, complement factor H–related protein CFHR1-5, multiplex ligation-dependent probe amplification
    - Presence of paraproteins that can activate the alternative complement pathway
- C3G may be subdivided into dense deposit disease (**DDD**) and **C3GN** based on EM findings. Both disease entities are thought to be a continuum of the same condition, both commonly present with proteinuria and low C3 levels, hematuria, and variable degrees of kidney function impairment.
  - **DDD**: characterized by electron-dense, osmophilic, elongated intramembranous deposits that replace GBM and mesangium with or without crescents. Patients may present with features of partial lipodystrophy and ocular drusen.

  - **C3GN** is characterized by mesangial, subendothelial, and, sometimes, subepithelial and intramembranous deposits. Features of DDD and C3GN may overlap.
- C4G is called C4 glomerulopathy. Its underlying cause remains to be determined.

MPGN with neither IC nor complement deposition

- May be seen with TMAs or other forms of endothelial injury
- Pathologic characteristics:
  - LM: Capillary wall or luminal fibrin may be present.
  - IF: no Igs or complements
  - EM: no electron-dense deposits. Subendothelial lucencies with or without luminal fibrin thrombi and capillary double contours
- Associated conditions: thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS), atypical HUS (aHUS), APS, drug-induced TMA, malignant HTN, radiation nephritis, bone marrow transplant–associated nephropathy, connective tissue disorders

Clinical manifestations

- Asymptomatic hematuria and proteinuria
- Acute nephritic syndrome
- NS
- CKD
- Rapidly progressive glomerulopathy

Diagnosis (see Figure 7.7)

- IC-MPGN: typically low C3 and C4
- Complement-mediated MPGN: typically low C3 and normal C4

Evaluation for IC-MPGN (ie, IF positive for Ig with or without complement deposits):

- Blood cultures, polymerase chain reaction, and serologic tests for viral (eg, hepatitis B, hepatitis C, cytomegalovirus [CMV]), bacterial, occult infections, malaria, and fungal infections (per local prevalence and/or symptoms)
- Cryoglobulins (consider rheumatoid factor: 70% cross-reactivity with cryoglobulins)
- Serum and urine protein electrophoresis and immunofixation, serum free light chain (FLC) (see **Appendix A7.5** for explanation of these tests)
- Screening for autoimmune disorders, particularly SLE
- Screening for malignancy, lymphomas, CLL

Evaluation for complement-mediated MPGN (ie, IF showing dominant complement deposits)

- Evaluate alternative complement pathway: serum complement levels, serum membrane-attack complex levels, alternative pathway functional assay, hemolytic complement assay.
- Retinal scan to evaluate for ocular drusen

- Consider genetic analysis for mutations and allele variants of complement factors and assays for the presence of autoantibodies to complement-regulating proteins, C3 nephritic factor.
- Evaluate for monoclonal gammopathy (particularly in individuals ≥50 years old).
- Rule out infection-related GN or PIGN prior to assigning the diagnosis of C3GN.

Evaluation for MPGN with neither Ig nor complement deposits: C3, CFH, ADAMTS13 (**A D**isintegrin **A**nd **M**etalloproteinase with a **T**hrombospondin type 1 motif, member **13**), blood smear for schistocytes, lactate dehydrogenase (LDH), indirect bilirubin, platelet count and volume

Management

- **Table 7.10** summarizes management strategies for MPGN arising from various etiologies. See **Appendix A7.6** for immunosuppressive regimens and dosing for active idiopathic MPGN.
- Specific therapy for MPGN depends on the underlying etiology if known.

Table 7.10 Management strategies for patients with MPGN pattern of injury

[a]Management strategies for patients with MPGN pattern of injury

Applicable to all patients with MPGN pattern of injury	Routine supportive therapy • ACEi/ARB for proteinuria as safely tolerated • Treat hypertension and lipids per routine CKD management if applicable. • Evaluate for secondary causes. • Treat underlying pathologic process if known (ie, infections, monoclonal gammopathy, autoimmune disease, malignancies).

[a]Idiopathic MPGN

Clinical manifestations		Additional therapy
Normal or near-normal kidney function with proteinuria	Proteinuria <3.5 g/d, no significant hematuria (ie, urinalysis with <10 RBC/HPF)	Supportive therapy alone (routine management above)
	Nephrotic syndrome with or without significant hematuria (ie, ≥10 RBC/HPF)	Limited course of GC trial
Abnormal kidney function active disease	Active urine sediment, with or without nephrotic range proteinuria, and no crescents	[b]GC and IST
	Rapidly progressive crescentic GN	[b]Treat with high-dose GC and CYC
Abnormal kidney function, indolent disease	Bland urine, variable degree of proteinuria	"Carefully" consider IST based on risks and benefits.
Abnormal kidney function, evidence of advanced kidney disease	Kidney biopsy with severe tubulointerstitial fibrosis or documented chronic kidney disease with eGFR <30 mL/min/1.73 m^2	Supportive therapy alone is suggested.

[c]C3 glomerulopathy

[a]Management strategies for patients with MPGN pattern of injury

Mild disease	Proteinuria <1.5 g/d	Supportive therapy only

Moderate-to-severe disease	Proteinuria ≥1.5 g/d and abnormal kidney function but without rapidly progressive disease	• Oral GC + MMF
		• If no improvement in kidney function or proteinuria after 6 mo:
		  • If positive genetic defect in factor H: trial of plasma infusion or plasma exchange.
		  • If no defect in factor H: switch to eculizumab or participate in clinical trial if available.

Rapidly progressive glomerulonephritis		• GC + CYC or MMF • Eculizumab may be considered in addition to IST.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CYC, cyclophosphamide; GC, glucocorticoid; GN, glomerulonephritis; IST, immunosuppressive therapy; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; RBC/HPF, red blood cell/high-power field.

[a]Management per KDIGO 2021.

[b]See **Appendix A7.6** Immunosuppressive therapy for patients with active idiopathic MPGN.

[c]Data from Kopel T, Salant D. C3 glomerulopathies: dense deposit disease and C3 glomerulonephritis. *UpToDate*. Accessed March 1, 2024. https://www.uptodate.com/contents/c3-glomerulopathies-dense-deposit-disease-and-c3-glomerulonephritis

Kidney transplantation

- Very high recurrence rates (15%-50% for C3GN)
- DDD: universal recurrence; 50% allograft failure within 5 years

NEPHROTIC/HEAVY PROTEINURIC GLOMERULAR DISORDERS

Minimal Change Disease (MCD)

Background: MCD is the most common cause of NS in children (70%-90% of NS in children <10 years of age), 50% in older children, and 10% to 15% of primary NS in adults.

Pathogenesis

- Unclear but thought to involve both T-cell and B-cell dysfunction
  - Evidence for T-cell dysregulation:
    - MCD improves with measles (known to modulate cell-mediated immunity).
    - MCD may be seen in patients with Hodgkin disease.
    - Atopic individuals are at higher risk for MCD.
    - Glomerular permeability factors such as T-helper type 2 (Th2)-derived cytokines (eg, IL-13). IL-13 induces CD80 expression, which in turn induces podocyte foot process effacement (FPE) and proteinuria. Notably, allergic states are associated

with IL-13 and MCD. Another suggested glomerular permeability factor is the circulating heme scavenger hemopexin.

- Evidence for B-cell dysfunction:
  - RTX may improve steroid-sensitive disease, suggesting a possible role for a glomerular permeability factor produced by B or T cells through pathways regulated or stimulated by B cells.
  - In a subset of patients with primary MCD, autoantibodies targeting the slit diaphragm component nephrin may contribute to the pathogenesis of disease. Punctate IgG deposits in podocyte cytoplasm co-localized with nephrin may be seen on IF microscopy.
- Alterations in GBM (ie, loss of negative charges induced by circulating factor)
- Defect/alterations of key proteins in slit diaphragm (eg, mutation of *NPHS2* gene [podocin])

Clinical manifestations

- The classic presentation of MCD is sudden onset of edema (ie, days to weeks) as opposed to slowly progressive edema seen with MN and most forms of FSGS, except the tip variant.
- NS
- Microscopic hematuria is seen in 20% to 25% in children, but more commonly in adults.
- AKI at presentation is common and often improves with diuresis, treatment of anasarca. Renal vein thrombosis should also be considered.

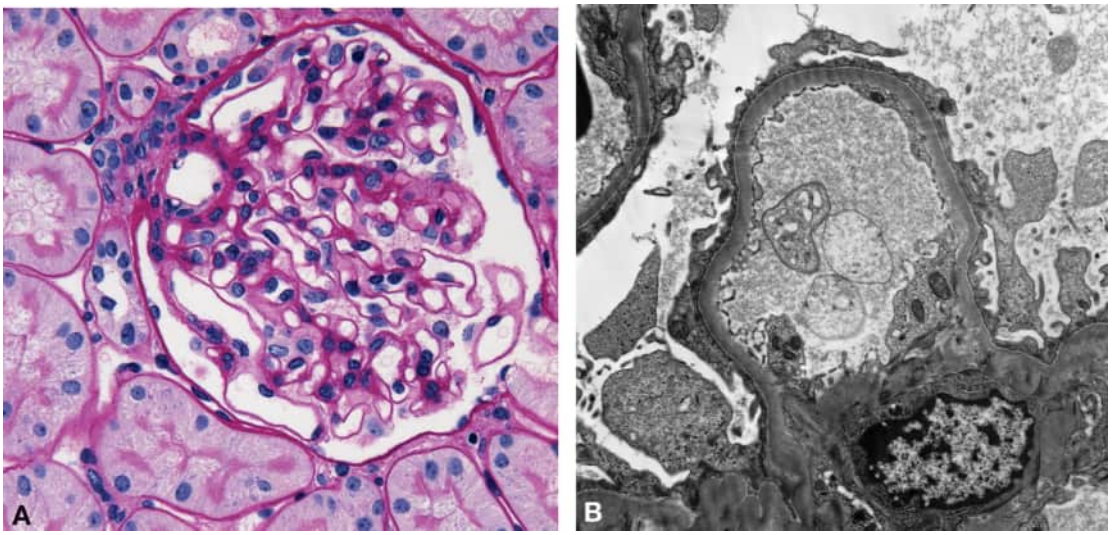
Clinical conditions associated with MCD

- Malignancies: Hodgkin, non-Hodgkin lymphoma, leukemia, rarely solid organ tumors
- Allergy, atopy, insect/bee stings, pollens, house dust
- Immunizations
- Drugs: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (long-term use), pamidronate, alendronate (both bisphosphonates are also associated with collapsing FSGS), lithium, D-penicillamine, tiopronin, γ-interferon, sulfasalazine and 5-aminosalicylic acid derivatives, antimicrobials (rifampin, penicillin derivatives), trimethadione, mercury exposure in skin-lighting creams and immune checkpoint inhibitors (pembrolizumab, ipilimumab, nivolumab, durvalumab)
- Infections: syphilis, tuberculosis, *Mycoplasma*, ehrlichiosis, hepatitis C virus (HCV), *Echinococcus*, borreliosis (Lyme disease), and HIV

Histopathology (Figure 7.9):

MCD is diagnosed by kidney biopsy in adults.

LM: Normal glomeruli


A
B

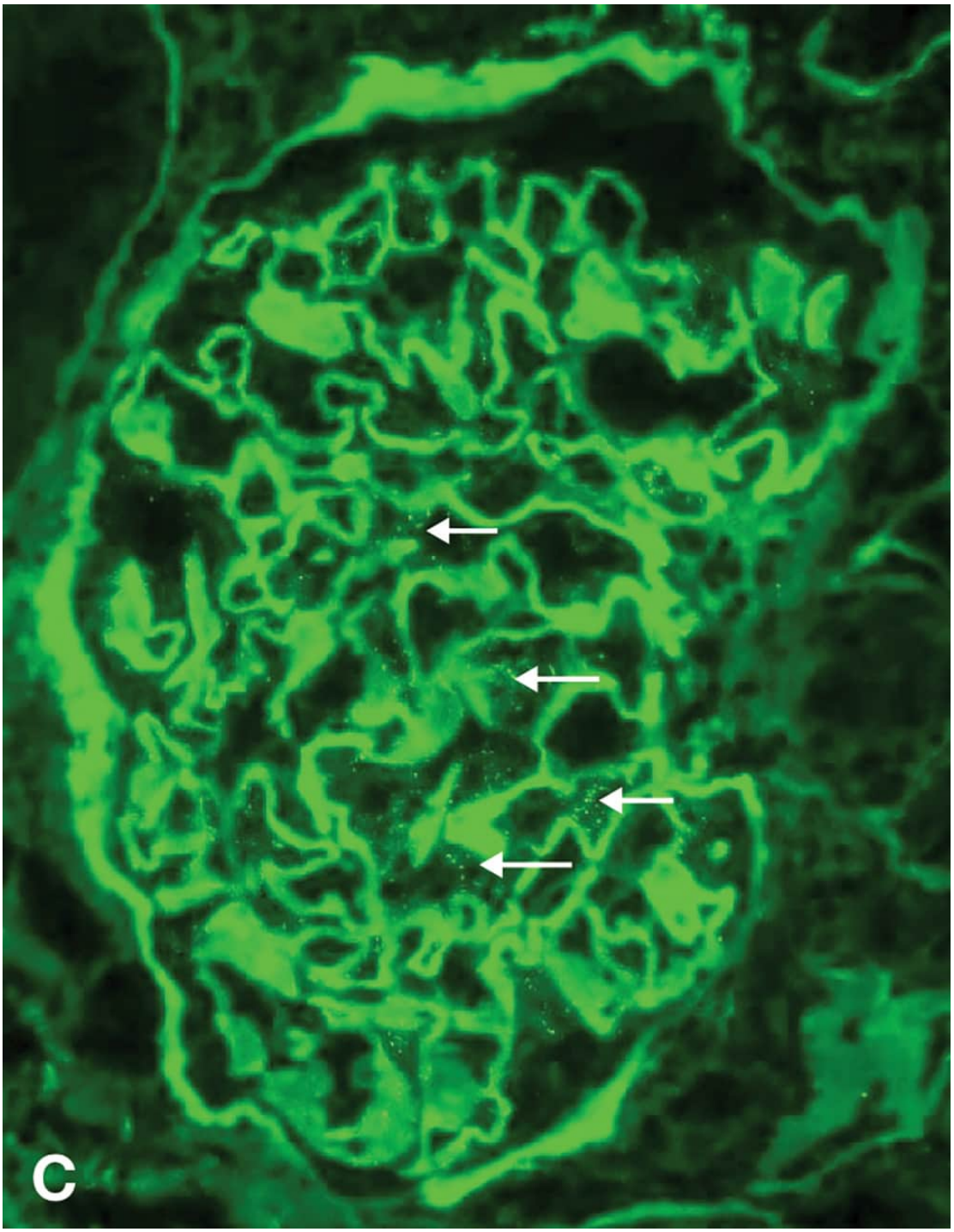


FIGURE 7.9 **Minimal change disease.** A. Normal glomerulus (periodic acid-Schiff ×400). B. Extensive podocyte foot process effacement over normal capillary basement membrane (×14,000). C. Podocyte finely granular "dusting" (arrows) for immunoglobulin G (×400).

- Tubules may have acute injury and luminal proteinaceous material due to heavy proteinuria.
- Glomerulopathies that may present with minor changes on LM as MCD include IgM nephropathy (IgMN), C1q nephropathy (C1qN), and minimal mesangial LN. Early

recurrence of primary FSGS in a kidney transplant may also present as MCD on LM.

- IgMN is an idiopathic glomerulopathy characterized by diffuse mesangial deposition of IgM with or without mesangial hypercellularity and mesangial electron-dense deposits on EM. The prevalence of IgMN among unselected biopsies has been estimated to be 2% to 5%. Clinically, IgMN spans the spectrum of MCD and FSGS. Treatment is similar to MCD/FSGS due to the lack of data.
- C1qN is a rare and idiopathic glomerulopathy characterized by dominant or co-dominant C1q mesangial deposition in the absence of clinical or immunologic features of SLE. LM features include MCD, FSGS, or proliferative GN. Clinical manifestations, management, and prognosis generally reflect LM features.

IF: no Ig or complement deposition
EM: podocyte FPE (>75%)

Management of MCD (KDIGO 2021)

Initial episode:

- Initial therapy should start with high-dose GC (eg, prednisone 1 mg/kg/d, maximum 80 mg/kg/d) for a minimum of 4 weeks and a maximum of 16 weeks. After remission, taper over at least 24 weeks.
- Consider CYC, CNI, or MPAA in patients with GC intolerance or contraindication.

Relapsing or steroid-dependent MCD:

- For infrequent relapses, consider prednisone 20 to 30 mg/d or short course of CYC.
- For frequent relapses or steroid-dependent (ie, ≥2 relapses within 6 months or ≥4 within 12 months) or steroid-dependent patients (2 relapses on steroid taper or within 1 month of ending therapy)
  - Consider CYC (if no previous CYC treatment) or CNI, MMF, or RTX (if previous CYC, intolerance to CYC, or patient preference).
  - In patients with frequent/steroid-dependent MCD who respond to RTX, RTX 1 g every 6 months for 2 to 3 years may be considered to prevent relapse (expert opinion).

See **Appendix A7.7** for dosing and comments on ISTs in MCD.

Supportive therapy:

- For severe AKI, concurrent temporizing kidney replacement therapy may be necessary.
- Statins should not be used to treat hyperlipidemia as risk of coronary artery disease is not increased with MCD. The benefit of statin's anti-inflammatory property is not proven.
- ACEi or ARBs use is *not* suggested in normotensive individuals for the *sole purpose* of lowering proteinuria in MCD unless proteinuria is anticipated to be protracted.

NOTE

In case of steroid resistant or frequent relapsing MCD, consider erroneous diagnosis due to poor tissue sampling. Rebiopsy to evaluate for FSGS should be considered.

Membranous Nephropathy (MN)

Epidemiology

- Less than 5% in children and 15% to 50% in adults with NS
- Male-to-female ratio is 2:1, more common in White males over the age of 40 years

Diagnosis

- A kidney biopsy is needed to diagnose MN in cases with negative anti-phospholipase A2 receptor (anti-PLA2R) antibodies or NS with unexplained AKI/rapid progression, regardless of anti-PLA2R status.
- In patients with significant contraindications or resistance to undergoing a biopsy, the presence of plasma anti-PLA2R antibodies is sufficient to diagnose and treat MN, especially if the eGFR is within the normal range. Nonetheless, it must be noted that a serologic diagnosis cannot provide glomerular, tubulointerstitial, and vascular histopathologies or prognostic information.

Histopathology (Figure 7.10)

LM:

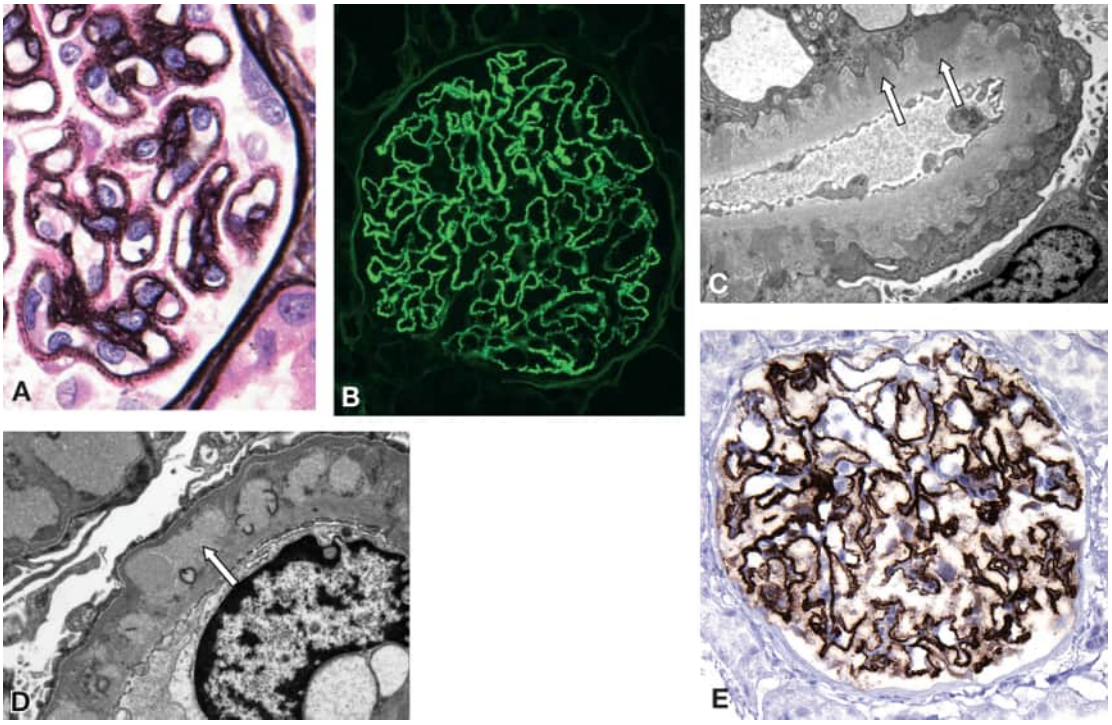


FIGURE 7.10 Phospholipase A2 receptor (PLA2R)-positive ("primary") membranous nephropathy. A. Global subepithelial deposits with intervening spikes of basement membrane material (Ehrenreich and Churg stage 2) (Jones silver ×600). B. Immunofluorescence for immunoglobulin G showing granular capillary wall staining (×400). C. Subepithelial electron-dense deposits (arrows) with intervening spikes of basement membrane material (×14,000). D. Predominantly cleared intramembranous deposits (arrow) with new subepithelial layer of basement membrane material in stage 4 disease (×14,000). E. Antibody to PLA2R staining in capillary wall deposits (×400).

- Variably thick capillary walls; no hypercellularity or inflammatory changes
- Methenamine (Jones) silver staining: projections of GBM between subepithelial deposits giving a characteristic spike-like pattern (stage 2). Resorption of subepithelial and intramembranous immune deposits leads to GBM thickening with lucencies or double contours (stages 3-4).
- Glomerular capillary leukocyte infiltration may occur in association with malignancy; polymorphonuclear leukocytic infiltrates with renal vein thrombosis.
- Concurrent FSGS is present in up to 30% and may portend worse prognosis (eg, rapid progression and poor response to therapy).
- Tubulointerstitial injury and fibrosis are common; may indicate advanced disease.

EM:

- Diffuse subepithelial granular electron-dense deposits that parallel IgG staining
- In primary MN, deposits are not seen in mesangial or subendothelial sites, whereas in secondary MN, there may be mesangial hypercellularity and deposits are often also present in mesangial and/or endothelial sites.
- FPE

IF: IgG and complement component deposits

- Generally, staining for IgG4 predominates in primary MN, whereas IgG1, IgG2, and/or IgG3 predominate in secondary MN, although this has been modified with identification of MN antigens.
- C3 is present in approximately 50% of patients and likely reflects active, ongoing immune deposit formation and complement activation. C1 and C4 are usually absent, indicating involvement of alternative or lectin pathways in association with podocyte injury. Minimal C3 staining suggests inactive or very early disease.
- Strong capillary staining for C1q, C3, IgG, IgM, and IgA, a.k.a. "full house," is associated with membranous lupus.

Pathogenesis

Antibody-*antigen* (Ab-Ag) complex formation or deposition at podocyte foot process base leads to complement activation and formation of C5b-9.

- The Ab-Ag complexes are capped and shed to form subepithelial deposits. C5b-9 complexes (a.k.a. membrane-attack complexes) are incorporated into multivesicular bodies and transported by podocyte into urinary space.
- Increased intracellular sublytic levels of C5b-9 activate podocytes, leading to the release of oxidants and proteases that cause GBM injury.

MN may be associated with the formation of antibodies against specific *self-antigens*

- M-type PLA2R:
  - PLA2R is a transmembrane podocyte protein.
  - Anti-PLA2R antibodies are present in 50% to 80% of patients with MN and are predominantly of the IgG4 subtype. In MN, the PLA2R antigen-antibody complex distributes along the GBM.

  - Anti-PLA2R titer correlates with disease activity.
  - Anti-PLA2R titer predicts outcome: Lower titer is associated with better rate of spontaneous remissions and time to remission in those requiring therapy.
  - Of interest, hepatitis B has been associated with PLA2R-positive membranous GN, especially among Chinese patients.
- Antibodies to neural epidermal growth-like factor-1 (NELL-1) antigen are responsible for approximately 5% to 10% of MN, the second most common antigen after PLA2R. There is often segmental capillary wall IC deposition and is IgG1 dominant. NELL-1 is associated with malignancy in 10% to 33% of cases and also associated with α-lipoic acid use and mercury exposure.
- Thrombospondin type 1 domain-containing 7A antigen (THSD7A) (2%-4% of MN): Approximately 15% of patients with THSD7A membranous GN may have an associated neoplasm, and it is IgG4 dominant.
- Exostosin-1 and exostosin-2 have also been implicated as target antigens of MN in adults. Exostosins are glycosyltransferases responsible for the synthesis of the heparin sulfate backbone that add glycosaminoglycan residues to the core protein, resulting in the generation of complex polysaccharides in the GBM. Exostosins are associated with systemic diseases, such as SLE or Sjögren disease.
- Rarely, neonates of parents whose fathers express neutral endopeptidase (NEP) but whose mothers are null for NEP have been born with MN and NS due to the transplacental passage of maternal anti-NEP antibody.
- Many other antigens-associated MN have been reported (see suggested reading list).
- Autoimmune diseases (dysregulated autoantibody formation against self-antigen): SLE, rheumatoid arthritis, mixed connective tissue disease, dermatomyositis, ankylosing spondylitis, Crohn disease, graft-versus-host disease, temporal arteritis, Sjögren, bullous pemphigoid, autoimmune thyroid disease

MN may be associated with the formation of antibodies against non-self antigens:

- Infectious antigens (eg, chronic active infections): hepatitis B (presence of hepatitis B surface antigen [HBsAg], hepatitis B core antigen [HBcAg], and usually hepatitis B e antigen [HBeAg]), hepatitis C, syphilis, tuberculosis, HIV, enterococcal endocarditis, leprosy, filariasis, malaria, schistosomiasis, hydatid disease
- Drugs/toxin antigens: captopril, gold penicillamine, NSAIDs, COX-2 inhibitors, hydrocarbons, mercury, formaldehyde, lithium, clopidogrel, alemtuzumab (for multiple sclerosis [MS] treatment), anti-TNF agents, immune checkpoint inhibitors
- Malignancies (tumor antigen): solid organs (lungs, GI, breast, kidney, etc)
- Cationic bovine serum albumin (cBSA) is a prominent antigen in childhood.

Clinical manifestations:

- Gradual onset (as opposed to acute onset in MCD and often FSGS tip variant)
- NS (60%-80%), benign urinary sediment, microscopic hematuria (25%-50%)
- Complement levels are typically normal but can be low in approximately 50% of hepatitis B virus (HBV)-associated MN.

Natural history of MN:

- One-third rule for (primary) MN: One-third achieves spontaneous remission, one-third remains the same, one-third slowly progresses to renal failure.
- Risks for disease progression:
  - Very high risk: life-threatening NS *or* rapid deterioration of kidney function not otherwise explained
  - High risk: eGFR less than 60 mL/min/1.73 m^2 and/or proteinuria greater than 8 g/d for greater than 6 months *or* normal eGFR, proteinuria greater than 3.5 g/d, not reduced by than 50% after 6 months of conservative therapy with ACEi/ARB and at least one of the following: serum albumin less than 2.5 g/dL, PLA2R antibody greater than 50 RU/mL, urinary α1-microglobulin greater than 40 µg/min, urinary IgG greater than 1 µg/min, urinary β2-microglobulin greater than 250 mg/d, or selectivity index greater than 0.2
  - Moderate risk: normal eGFR, proteinuria greater than 3.5 g/d, not reduced by than 50% after 6 months of conservative therapy with ACEi/ARB and not fulfilling high-risk criteria. The presence of serious complications of NS (eg, AKI, infections, thromboembolic events) justifies increasing the risk profile of patients with 4 to 8 g proteinuria from medium to high risk.
  - Low risk (<5% chance of progression): normal eGFR, proteinuria less than 3.5 g/d, and serum albumin greater than 3 g/dL or a reduction of more than 50% after 6 months of conservative therapy with ACEi/ARB
- Progression/outcome of secondary MN: Resolution may occur within 1 week (NSAIDs) to years (gold, penicillamine) following withdrawal of inciting agent/condition.
- Complications/conditions associated with MN:
  - Dyslipidemia increases CV risk, particularly if remission cannot be achieved.
  - Up to 5 times increased incidence of associated malignancy especially in those older than 65 years, particularly, but not exclusively, in MN not caused by antibodies to PLA2R
  - Increased risk for thromboembolic disease (eg, deep vein thrombosis, renal vein thrombosis, pulmonary embolism [40%])

Management of MN (KDIGO 2021)

Routine care

Optimize use of ACEi/ARB, BP control, and statin (as needed for dyslipidemia).

Evaluation for secondary causes

- Chronic infections: hepatitis C, hepatitis B, HIV, treponemal infections
- History of drug use (eg, NSAIDs, gold, penicillamine)
- Malignancy screen per age, gender, and personal risks: Patients with MN should be evaluated for underlying malignancy *independent of* the presence or absence of anti-PLA2R antibodies, anti-THSD7A, or any other antibodies (ie, chest radiograph or computed tomography [CT] for lung carcinoma/sarcoidosis, breast and colon cancer screening, kidney ultrasound, urine cytology, mammography, upper endoscopy, colonoscopy, prostate-specific antigen with ultrasound and biopsy as indicated).

Anticoagulation

- Full anticoagulation with warfarin is recommended for the duration of the NS for patients with known thromboembolic events. Low-dose low-molecular-weight heparin (LMWH) plus aspirin for 3 months prior to switching to warfarin may be considered, to allow for treatment/improvement of NS.
- Prophylactic anticoagulation therapy with oral warfarin (with heparin bridging) may be considered for MN patients with NS and high thromboembolic risks (see "General management considerations for glomerular/vascular diseases" section). It is reasonable to maintain anticoagulation over the duration of the NS.
- Patients with MN and NS are also at risk for developing arterial thrombotic events. Risks include age, history of previous events, diabetes, eGFR, smoking, and severity of NS.
- GCs increase the risk of thrombosis.
- Risk of bleeding must be evaluated (see University of North Carolina, School of Medicine: Prophylactic Anticoagulation in Patients with Membranous Nephropathy online calculator) prior to anticoagulation.

Indications for IST

- Patients with MN but *without NS*: Immunosuppression is not necessary for patients with MN, proteinuria less than 3.5 g/d, serum albumin greater than 3 g/dL by bromocresol purple or immunometric assay, and eGFR greater than 60 mL/min/1.73 m^2.
- Patients with MN and *with NS*:
  - IST is not required in patients with MN, NS, and normal eGFR, unless at least one risk factor for disease progression is present or serious complications of NS (eg, AKI, infections, thromboembolic events) have occurred.
  - IST should be restricted to patients at moderate or worse risk for progressive kidney injury. See risk stratifications defined previously.

Immunosuppressive therapies (KDIGO 2021)

Table 7.11 summarizes immunosuppressive strategies for primary MN.

Table 7.11 Immunosuppressive therapy suggestions for primary membranous nephropathy based on risk of disease progression (KDIGO 2021)

Progression risk	Risk-defining factors	Immunosuppression	Comments
Very high	Life-threatening NS ***or*** Rapid eGFR deterioration not otherwise explained	CYC + GC *or* RTX	High or very high risk: Cyclical therapy with a cytotoxic agent. [a]CYC + GC is the preferred initial therapy.
High	eGFR <60 mL/min/1.73 m^2 ± proteinuria >8 g/d for >6 mo ***or*** Normal eGFR, proteinuria >3.5 g/d not decreased by >50% after 6 mo of ACEi/ARB and ≥1 of the following:	RTX *or* CYC + GC *or* CNI + RTX	In patients with high risk of progression, add RTX after 6 mo of CNI unless negative anti-PLA2R antibody after CNI treatment.

Progression risk	Risk-defining factors	Immunosuppression	Comments
	• Serum albumin <2.5 g/dL • Serum anti-PLA2R >50 RU/mL • Urine: a1-microglobulin >40 mg/min, IgG >1 mg/min, β_2-microglobulin >250 mg/d, or selectivity index >0.2		
Moderate	• Normal eGFR, proteinuria >3.5 g/d not decreased by >50% after 6 mo of therapy with ACEi/ARB and not fulfilling high-risk criteria. • The presence of serious complications of NS (eg, AKI, infections, thromboembolic events) justifies increasing the risk profile of patients with 4-8 g proteinuria from medium to high risk.	Wait & see *or* RTX *or* CNI ± GC	• RTX is the preferred first-line IST for moderate risk of disease progression. • CNI may be considered for moderate disease progression risk and normal eGFR when RTX is not tolerated or available. CNI is often given with prednisone 10 mg/d. • Withdraw therapy if no response after 4 mo. Taper after 12 mo. CNI may be continued for 24 mo for possible lower relapse rate.
Low risk (<5% chance of progression)	Normal eGFR, proteinuria <3.5 g/d, and serum albumin >3 g/dL ***or*** A decrease of >50% after 6 mo of therapy with ACEi/ARB	Wait & see	• Control BP and maximize RASi. • Monitor disease progression: Modify therapy per disease progression risk over 3-6 mo.

See **Appendix A7.8** for dosing.

[a]CYC is preferred over chlorambucil due to the latter's greater side-effect profile.

Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; AKI, acute kidney injury; anti-PLA2R, anti-phospholipase A2 receptor antibody; BP, blood pressure; CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; IgG, immunoglobulin G; IST, immunosuppressive therapy; KDIGO, Kidney Disease: Improving Global Outcomes; NS, nephrotic syndrome; RASi, renin-angiotensin inhibitors; RTX, rituximab.

- Very high risk: RTX *or* (CYC + GC)—see **Appendix A7.8** for dosing
- High risk: RTX *or* (CYC + GC) *or* (CNI + RTX)
  - In patients with high risk of progression, add RTX after 6 months of CNI unless negative anti-PLA2R antibody after CNI treatment.
  - In high- or very high-risk patients who develop deteriorating kidney function due to MN and for whom IST is felt to be appropriate, cyclical therapy with a cytotoxic agent (CYC is preferred to chlorambucil due to the latter's greater side-effect profile) plus GC is the preferred initial therapy.
- Moderate risk: "wait and see" *or* RTX *or* (CNI ± GC)
  - RTX is the preferred first-line IST for patients with moderate risk of disease progression.

    - CNI may be considered in patients with moderate risk for disease progression and in individuals with normal eGFR and RTX is not tolerated or available.
- Low risk: "wait and see," optimize BP control, maximize the use of renin-angiotensin inhibitors

Focal and Segmental Glomerulosclerosis (FSGS)

Background

- FSGS refers to a morphologic pattern of glomerular injury that may arise from a primary podocytopathy, a genetic mutation, a secondary adaptive process involving nephron mass reduction, reflux nephropathy, viral or drug toxicity, or other glomerular disease, or an undetermined process.
- Basic histopathologic findings of FSGS: Segmental increase in mesangial matrix with obliteration of capillaries, sclerosis, hyalinosis, foam cells, podocyte hypertrophy with or without hyperplasia, and adhesions between glomerular tuft and Bowman capsule are common to all four FSGS etiologies.

> **NOTE**
>
> The deep inner juxtamedullary glomeruli are preferentially affected in early primary FSGS. Renal biopsies containing less than 15 glomeruli or only more superficial cortical glomeruli may be insufficient to exclude FSGS.

- FSGS is now the most common cause of NS and GN-related ESKD in adults in the United States, excluding diabetic kidney disease (DKD).

Primary FSGS

- Refers to primary podocytopathy (ie, primary alterations of glomerular epithelial cells)
- Usually presents with sudden onset edema and proteinuria
- Typical presentation: proteinuria greater than 3.5 g/d, serum albumin less than 3.0 g/dL, with or without edema
- Widespread podocyte FPE of nonsclerotic glomeruli can be seen on EM.

Secondary FSGS

- Refers to FSGS changes secondary to an independent glomerular injury process or disease
- Development of edema and proteinuria are usually slowly progressive.
- Does not typically present with NS
- EM generally reveals less than 80% segmental FPE of nonsclerotic glomeruli. However, collapsing FSGS secondary to HIV, other viruses, or drugs such as interferon or pamidronate/alendronate may be characterized by widespread FPE.

Genetic inheritance/predisposition to FSGS

- A large number of autosomal dominant and recessive genes inherited with variable penetrance have been identified that can cause FSGS. Genetic testing may be beneficial for some individuals, predominantly to avoid GC, as most are steroid resistant. Mutations in phospholipase C epsilon 1 (PLCε1) may be an exception.

- Genetic FSGS may have minimal to more than 80% FPE depending on the location and function of the affected gene.
- Inheritance of two polymorphic risk alleles (G1, G2) of the apolipoprotein 1 gene (*APOL1*) increases the risk of FSGS, as well as the risk of progressive functional decline in patients with non-DKD. These polymorphisms are more common in individuals of more recent African ancestry. APOL1 polymorphisms protect against *Trypanosoma brucei*, a parasite spread by tsetse flies in Africa.
- Missense APOL1 polymorphisms predispose patients to an excess risk of ESKD.
- The presence of APOL1 risk polymorphisms is not a contraindication for a trial of GC.

Pathogenic classification of FSGS

Primary (idiopathic) FSGS (1^0 FSGS)

- The recurrence of proteinuria and 1^0 FSGS following kidney transplantation, transient proteinuria in an infant born to a mother with 1^0 FSGS, and resolution of proteinuria in a retransplanted kidney from a recipient with 1^0 FSGS into a recipient without the condition all support the role of a circulating permeability factor in the pathogenesis of 1^0 FSGS.
- Antinephrin antibodies have been implicated as pathogenic in up to two-thirds of children and adults with primary FSGS and may be viewed as one of the sought-after circulating permeability factors. Other circulating permeability factor candidates, including soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine-1, angiopoietin-like 4, and CD80, remain to be independently validated.

Secondary FSGS

- Virus: HIV type-1 (established), CMV (probable), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (with APOL1 high-risk genotype), and, possibly, Epstein-Barr virus, parvovirus B19, hepatitis C
- Drugs: heroin (adulterants), interferons (α, β, and γ), lithium, pamidronate, alendronate, sirolimus, anabolic steroids (body builders), CNIs, anthracyclines, direct-acting antiviral (DAA) therapies
- Adaptive structural-functional responses
- Reduced kidney mass: low birth weight, oligomeganephronia, premature birth, unilateral kidney agenesis, reflux uropathy, chronic allograft nephropathy, advanced kidney disease with reductions in functioning nephrons
- Initially normal kidney mass: HTN, DKD, atheroemboli/acute vaso-occlusive process, obesity, increased lean body mass, cyanotic congenital heart disease, sickle cell anemia
- Malignancy (in particular lymphoma)
- Association with any underlying glomerular diseases: (IgAN, LN, pauci-immune focal necrotizing and crescentic GN), hereditary nephritis (Alport syndrome), membranous glomerulopathy, TMA, others

Genetic FSGS

- Familial/genetic: There are dozens of affected genes now reported, including nephrin (*NPHS1*), podocin (*NPHS2*), α-actinin 4, transient receptor potential cation 6 (*TRPC6*),

WT1, *SCARB2 (LIMP2)*, inverted formin-2 (*INF2*), CD2-associated protein (*CD2AP*), coenzyme Q2, *PLCε1*, mitochondrial cytopathies. With the possible exception of PLCε1, it is recommended to avoid immunosuppression in patients with genetic forms of FSGS.

- APOL1. Patients with APOL1-mediated kidney disease respond less than optimally to standard therapies, but they do respond at some level, and usual treatment should not be withheld. Harboring two APOL1 risk variants (G1/G1, G2/G2, or G1/G2) predisposes to FSGS and accelerates progression in most non-DKD. A strong protective/rescue effect has been described that is conferred by an *APOL1* p.N264K variant against G2-associated FSGS and kidney disease.

Histopathology of FSGS variants (Figure 7.11):

Perihilar FSGS:

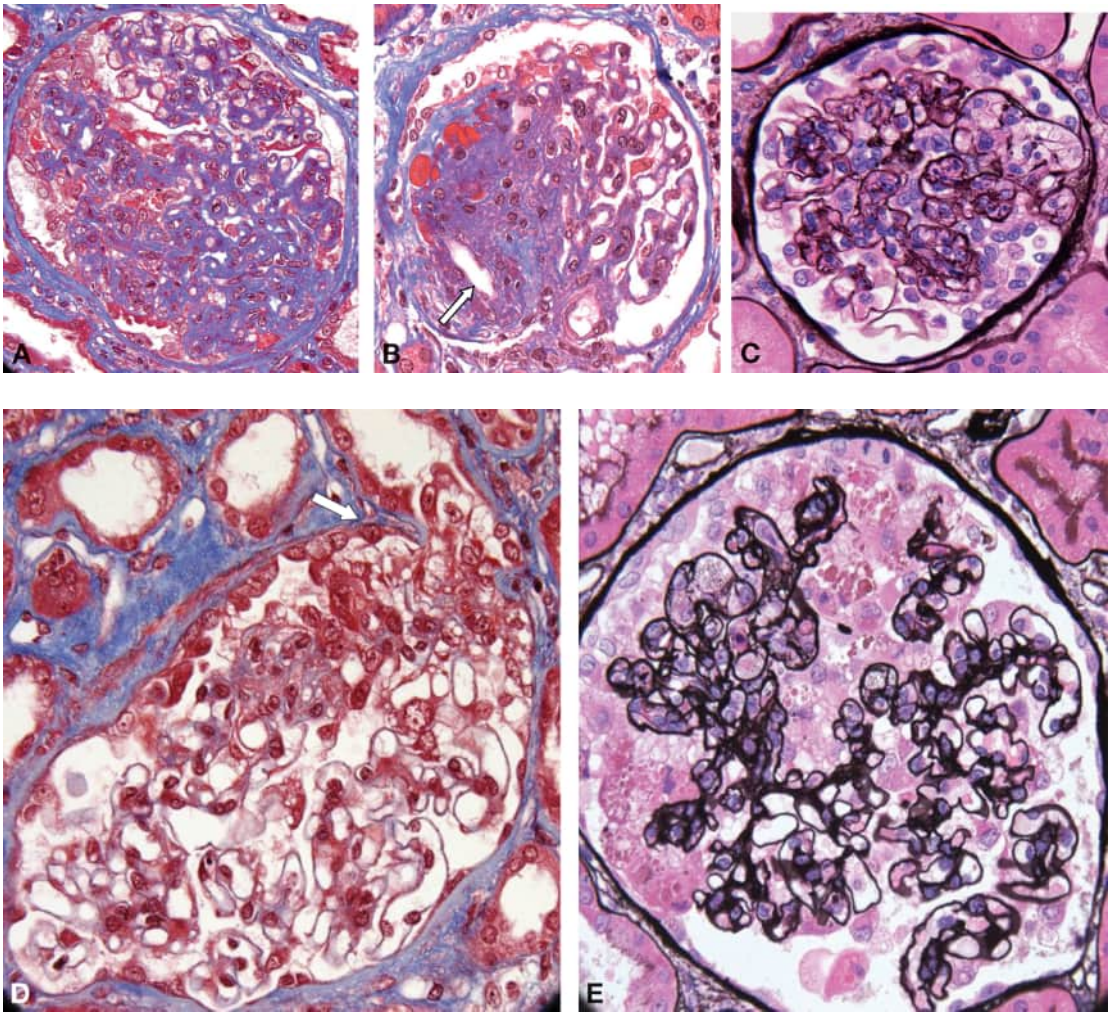


FIGURE 7.11 **Focal and segmental glomerulosclerosis.** A. Not otherwise specified variant. Segmental capillary obliteration, podocyte hypertrophy, adhesions to Bowman capsule, and insudative lesions not at the tip or perihilar region (Masson trichrome ×400). B. Perihilar variant. Segment of sclerosis is adjacent to the arteriolar pole (arrow) and characterized by capillary obliteration, insudative lesions (orange), and overlying halo formation (podocyte detachment with deposition of new light blue basement membrane material) (Masson trichrome ×400). C. Cellular variant. Segmentally, capillaries contain foam

cells and leukocytes in association with podocyte hypertrophy (Jones silver ×400). D. Tip lesion variant. Podocyte hypertrophy and capillary obliteration are adjacent to the tubular pole (arrow). Note the sclerotic segment protruding into the proximal tubular lumen (Mason trichrome ×400). E. Collapsing variant. Capillary wall collapse and luminal obliteration with visceral epithelial cell hypertrophy, hyperplasia, and cytoplasmic vacuoles and protein droplets (Jones silver ×400).

- Glomerulosclerosis at glomerular vascular pole, thought to reflect increased filtration pressures at the afferent arterioles associated with compensatory demand; glomerular hypertrophy; FPE is typically segmental and not severe.
- Associations: adaptive FSGS (see etiologies above)
- Clinical features: typically subnephrotic proteinuria and normal serum albumin levels

Cellular FSGS:

- Least common variant
- Expansile segmental lesion with endocapillary hypercellularity, often including foam cells and infiltrating leukocytes; variable glomerular epithelial cell hyperplasia
- Severe FPE is typically seen on EM.
- Associations: usually primary, but may be seen with secondary causes
- May represent early stage in the evolution FSGS or tip lesion without proper glomerular orientation
- Clinical features: typically NS

Tip lesion FSGS:

- Segmental lesion involving tubular pole, with either adhesion to tubular outlet or confluence of hypertrophic podocytes and tubular epithelial cells, may herniate into proximal tubules; foam cells often present.
- Compared with other variants, tip lesion has the least tubular atrophy and interstitial fibrosis; severe FPE is typical.
- Tip lesion is more common in White race.
- Associations: usually primary; thought to be mediated by physical stresses on paratubular segment due to convergence of protein-rich filtrate on tubular pole
- Clinical features: usually abrupt onset of NS; best prognosis, highest rate of response to GC compared to all other FSGS variants

Collapsing FSGS

- Implosive glomerular-tuft collapse with hypertrophy and hyperplasia of overlying epithelial cells; hyperplastic glomerular epithelial cells may fill urinary space, resembling crescents; severe tubular injury; tubular microcysts common; severe FPE
- Associations: primary, secondary, or genetic (coenzyme Q2 or Q6 mutations)
- Clinical features: most aggressive variant of primary FSGS, Black racial predominance and severe NS; worse prognosis, poor response to GC

Not otherwise specified (NOS) FSGS

- Generic form of FSGS, not meeting any variant above
- Associations: most common subtype, can occur with primary, secondary, or genetic forms; other forms can evolve into NOS over time.
- Clinical features: variable

- Usually segmental FPE

Evaluation for underlying etiology of FSGS

For patients presenting with NS, especially with severe FPE:

- Likely primary FSGS: Treat with IST.
- If collapsing FSGS, evaluate for underlying cause.
- If no response to IST, consider genetic testing.

For patients presenting with non-NS:

- Evaluate for secondary causes of FSGS. See differential diagnosis for secondary FSGS above.
- Consider genetic testing when appropriate (eg, strong family history for FSGS), no secondary cause can be identified, or when condition deteriorates into NS despite conservative therapy.

Management of FSGS

Supportive care for all FSGS variants

- Consider renin-angiotensin system inhibition, mineralocorticoid antagonists, BP control, volume control (low-Na diet, diuretics), CV risk reduction (statins, aspirin), and vitamin D (especially in children).
- The data for SGLT2i in FSGS are not compelling.
- Consider alkalinizing therapy to maintain serum bicarbonate in the range of 28 to 32 mEq/L to slow decline of kidney function.

Management of primary FSGS (See **Table 7.12**)

Table 7.12 Management of primary focal segmental glomerulosclerosis (KDIGO 2021)

Initial therapy for FSGS

Routine therapy for all forms of FSGS	RAAS inhibition and dietary sodium restriction. Consider alkalinizing therapy to maintain serum bicarbonate in the range of 28-32 mEq/L.	
First-line therapy for primary FSGS	Glucocorticoid (GC)	• Prednisone 1 mg/kg (max 80 mg) qd or 2 mg/kg (max 120 mg) qod for ≥4 wk • Initial high-dose GC should be continued until complete remission is achieved, or as tolerated up to a maximum of 16 wk, whichever is earlier. • In patients with persistent and unremitting proteinuria or GC intolerance, may taper off GC prior to 16 wk
[a]Alternative first-line therapy (for GC intolerance or nonresponders)	[b]Calcineurin inhibitor (CNI)	• Cyclosporine 3-5 mg/kg/d in 2 divided doses (target trough level: 100-175 ng/mL) or tacrolimus 0.05-0.1 mg/kg/d in 2 divided doses (target trough level: 5-10 ng/mL) × ≥6 mo • Treat for ≥6 mo at target levels before considering CNI nonresponder. • Discontinue CNI if GFR continues to decline <30 mL/min/1.73 m^2.

Initial therapy for FSGS

Other options lacking robust evidence and/or established dosing include RTX, MMF, and repository corticotropin injection (Acthar gel).

Follow-up management in 8-16 wk

[c]GC-induced complete response (CR)	Reduce prednisone by 5 mg every 1-2 wk to complete a total duration of 6 mo.	
[d]GC-induced partial response (PR) at 8 wk	→ Continue GC for up to 16 wk.	If CR is achieved by 16 wk → Reduce prednisone by 5 mg every 1-2 wk to complete a total duration of 6 mo.
		If PR and 24-h urine protein <1.5 g/d at 8-16 wk → Maximize nonimmunosuppressive therapy and observe.
		If PR and 24-h urine protein >1.5 g/d at 16 wk → Switch therapy to CNI.
[e]No remission with GC	No remission with GC by 8 to 16 wk → Taper GC and switch to CNI (see CNI dosing above)	
CNI responders	• Continue for at least 12 mo to prevent relapse on withdrawal. After the first 12 mo, taper CNI over 6-12 mo. • Discontinue CNI if GFR continues to decline below 30 mL/min/1.73 m^2.	

Problematic cases

Frequent relapse or GC dependent	Frequent relapse of GC dependent (two relapses or relapse during or within 2 wk of completing GC therapy) → Treatment is similar to that for relapsing MCD in adults.
No remission by 6 mo	• [f]No remission by 6 mo → Discontinue therapy and consider referral for participation in a clinical trial. • Consider other options lacking robust evidence and established dosing including RTX, MMF, and repository corticotropin injection (Acthar gel).

Abbreviations: CNI, calcineurin inhibitor; CR, complete remission; DM, diabetes mellitus; GC, glucocorticoid; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; PR, partial remission; RAAS, renin-angiotensin aldosterone system; RTX, rituximab.

[a]Alternative therapy may be considered if there is intolerance or contraindications to glucocorticoid use (eg, uncontrolled DM, psychiatric conditions, severe osteoporosis). Note, RTX is emerging as a valuable agent to treat primary FSGS, with robust responses even in patients with frequently relapsing or steroid-dependent disease. Some experts consider RTX as a preferred alternative to GC over CNI. Optimal RTX dosing for FSGS has not been firmly established.

[b]Occasionally, patients will respond to either cyclosporine or tacrolimus, but not both. If there is no response to one, assess sensitivity to the other. cyclosporine is thought to exert an antiproteinuric effect on the podocyte cytoskeleton (synaptopodin), independent of its immunosuppressive effect. Tacrolimus may act on the podocyte TRPC6 channel.

[c]Complete remission (CR, proteinuria <0.3 g/d, normal SCr, and serum albumin > 3.5 g/dL).

[d]Partial remission (PR, proteinuria 0.3 to <3.5 g/d, stable SCr or change in SCr by <25%).

[e]No remission (ie, proteinuria without response or declined but still >3.5 g/d).

[f]Consider clinical trials: NephCure Kidney International. Clinical trials. Accessed July 15, 2024. https://kidneyhealthgateway.com; National Kidney Foundation. Kidney diseases clinical trial directory. Accessed July 15, 2024. https://www.kidney.org/atoz/content/how-can-i-find-clinical-trial; and Glomerular Disease Consortium. Clinical trials. Accessed July 15, 2024. https://www.enrollmypatient.org/

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1-S276.

- Few patients with primary FSGS will respond optimally to supportive care alone. Immunosuppression is usually required.
- Prednisone (~1 mg/kg up to 80 mg daily or 2 mg/kg up to 120 mg every other day for at least 4 weeks) remains the initial treatment choice for patients with primary FSGS unless there are absolute or relative contraindications.
  - GC taper can be initiated if there is a CR in proteinuria at or before 16 weeks.
  - If there is a reduction in proteinuria at 8 weeks, but the patient has not reached CR, the initial steroid dose should be maintained for a total of 16 weeks prior to taper.
  - If no reduction in proteinuria is seen at 8 weeks, additional or alternative therapies should be initiated.
- For patients with absolute or relative contraindications to GC use, CNI or RTX is advised. Emerging evidence supports the use of these agents as first-line therapy for some, even in the absence of GC contraindications.
  - Consider CNI in patients with intolerance or contraindications to GC use (eg, uncontrolled diabetes, psychiatric conditions, severe osteoporosis).
  - Occasionally, patients will respond to either cyclosporin or tacrolimus, but not both. If there is no response to one, assess sensitivity to the other.
    - Cyclosporine A is thought to exert an antiproteinuric effect on the podocyte cytoskeleton (synaptopodin), independent of its immunosuppressive effect.
    - Tacrolimus may act on the podocyte TRPC6 channel.
  - RTX is emerging as a valuable agent to treat primary FSGS, with robust responses even in patients with frequently relapsing or steroid-dependent disease.
  - MMF may also be effective in patients resistant to other agents.
- If there are frequent relapses or steroid-dependent FSGS (two relapses or relapse during or within 2 weeks of completing steroid therapy), treatment is similar to that for relapsing MCD in adults. Relapse is defined as having proteinuria greater than 3.5 g/d after CR has been obtained. CYC, MMF, RTX, and CNI have all been reported to confer some benefit.

Management of secondary FSGS

- Adaptive FSGS: no IST; encourage healthy living including weight loss if obese, smoking cessation.
- Other: Treat underlying disease or removal of etiologic agents.

Management of genetic FSGS

- Patients with FSGS due to genetic mutations should be treated with RAASi, sodium restriction, BP control, and, possibly, bicarbonate, but not with immunosuppression.
- APOL1: Patients with two APOL1 risk polymorphisms (G1/G1, G2/G2, G1/G2) should be treated the same as patients with primary FSGS. Consider referral to an APOL1 clinical trial for patients with suboptimal response to therapy. Phase 2 and 3 clinical trials are now underway to test whether inhibiting APOL1 transcription or signaling in patients with two risk variants will reduce proteinuria and preserve renal function in patients with FSGS or HTN.

- Patients with FSGS associated with the very rare primary Coenzyme Q10 deficiency due to CoQ2, Q6, or Q8b mutations, may respond to Coenzyme Q10 supplementation.

Kidney transplantation

- Recurrence occurs in 17% to 50% of primary FSGS.
- Risks for recurrence:
  - Younger age (eg, children)
  - Non-Black race
  - Rapid course of ESKD (<3 years in native kidneys)
  - Heavy proteinuria prior to transplantation
  - Loss of previous allografts to recurrence
- Little chance of recurrence for most genetic forms, as the defect is in the native kidney and not the allograft.
- Live renal donors who have two APOL1 risk polymorphisms may be at higher risk of subsequent HTN, proteinuria, and CKD. Transplant kidney survival from deceased donors with two APOL1 risk polymorphisms may also be reduced. Two large studies evaluating this are in progress (APOLLO and LETO). Using prospective and retrospective data collection, these studies are anticipated to provide much-needed data on the effect of APOL1 risk variants on donor and recipient outcomes. Also see **Chapter 9: Kidney Transplantation**.

PARAPROTEIN-RELATED DISORDERS

Kidney Manifestations in Paraprotein-Related Disorders

Kidney disease can be caused by paraproteins produced in MM, B-cell lymphoproliferative disorders, Waldenström macroglobulinemia, CLL, or monoclonal gammopathy of renal significance. Depending on the characteristics of the paraproteins (ie, κ or λ LC or heavy chain [HC]), biochemical milieu (eg, surrounding pH, ionic strength, urine flow), and associated complications or treatment, kidney injuries may arise due to:

- direct tubular toxicity,
- aggregation of paraproteins in tubular lumen causing intratubular obstruction,
- direct deposition in kidney tissues,
- inflammatory response to the presence and/or processing of paraproteins,
- associated electrolyte, volume, and blood viscosity abnormalities,
- nephrotoxic diagnostic study, and/or
- reactions to treatment of the underlying paraproteinemia.

Table 7.13 summarizes kidney manifestations in paraprotein-related disorders.

Table 7.13 Kidney injury patterns related to paraproteinemia

	Plasma cells	Light chain (LC)	Heavy chain (HC)	Processed LC/HC	Inflammatory response	Treatment related
Tubules	Infiltrative disease	• Cast nephropathy • Fanconi syndrome; proximal tubulopathy • TBM deposition (MIDD)		• Amyloidosis • Immunotactoid GN (rare)	• Acute tubular injury/necrosis (eg, volume depletion, intravenous radiocontrast, NSAIDs) • Tubulointerstitial nephritis (eg, drug-induced, hypercalcemia- or hyperuricemia-induced tubulointerstitial injury)	
Interstitium		• LC or HC or both LC/HC deposition disease • Monoclonal cryoglobulinemia, IgM deposition				
Glomeruli					• MPGN • PGNMID • FSGS • MCD (rare) • TMA (likely complement mediated)	Collapsing FSGS (bisphosphonates)
Capillaries						
Systemic	• Hypercalcemia (bone resorption) • Hyperuricemia (high turnover)	• Cardiorenal syndrome due to cardiac deposition and reduced EF • Rhabdomyolysis (deposition into muscles) • Hyperkalemia (from rhabdomyolysis) • Hyperphosphatemia (from bone resorption, increased tubular reabsorption of phosphate, and rhabdomyolysis)			• Hyperviscosity leading to ATI/ATN • Infection/sepsis related to chemotherapy	

Any condition that affects the glomeruli can lead to glomerular basement membrane injury and significant albuminuria. "Proteinuria mismatch" is present in cast nephropathy but not with GBM injury due to presence of high amount of albuminuria that can be detected by routine urine dipstick testing.

Abbreviations: ATI, acute tubular injury; ATN, acute tubular necrosis; EF, ejection fraction; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulopathy; HC, heavy chain; LC, light chain; MCD, minimal change disease; MIDD, monoclonal immunoglobulin deposition disease; MPGN, membranoproliferative glomerular injury; pattern; NSAIDs, nonsteroidal anti-inflammatory drugs; PGNMID, proliferative GN with monoclonal Ig deposits; TBM, tubular basement membrane; TMA, thrombotic microangiopathy.

Direct toxicity to tubules

Direct tubular toxicity may occur when paraproteins are filtered and reabsorbed by proximal tubules. Accumulation of FLC within proximal tubular cells can affect normal lysosomal function, promote the formation of reactive oxygen species, and activate the production of pro-inflammatory cytokines, thereby inducing cellular injury.

LC proximal tubulopathy (Fanconi syndrome)

- Proximal tubular injury may occur due to the reabsorption and accumulation of crystallized nondegradable variable domain fragments of the filtered monoclonal FLC.
- Patients may present with various proximal tubular transport defects, including proximal renal tubular acidosis (RTA), phosphate wasting, uricosuria (hence

hypouricemia), euglycemic glycosuria, and aminoaciduria.
- Distal tubular dysfunction may also be present.

Aggregation of paraproteins causing intratubular obstruction

LC (Bence Jones protein) cast nephropathy, a.k.a. "myeloma kidney":

- LC cast nephropathy is the most common renal presentation in patients with MM (30%-60%).
- LC cast nephropathy is considered a "myeloma-defining event."
- Cast nephropathy may also be seen in patients with Waldenström macroglobulinemia, lymphomas, and CLL.
- Proteinuria mismatch may be seen (see "Diagnosis of paraprotein-related disorders" section).

Pathogenesis of cast nephropathy

- Glomerular filtration of large amounts of monoclonal FLC produced by plasma cell clones in MM, or, less commonly, B-cell lymphoproliferative disorder, leads to intratubular cast formation, tubular obstruction and rupture, extravasation of monoclonal FLC into the interstitium, and subsequent interstitial inflammatory response and fibrosis.
- Factors promoting cast nephropathy: volume depletion, metabolic acidosis (promotes binding of FLC to uromodulin to form the casts), loop diuretics (increased luminal NaCl can promote cast formation by increasing the aggregation of FLC with locally secreted uromodulin), hypercalcemia-induced renal hypoperfusion (via renovasoconstriction and nephrogenic diabetes insipidus), NSAIDs, IV radiocontrast agent

Histopathology (**Figure 7.12**):

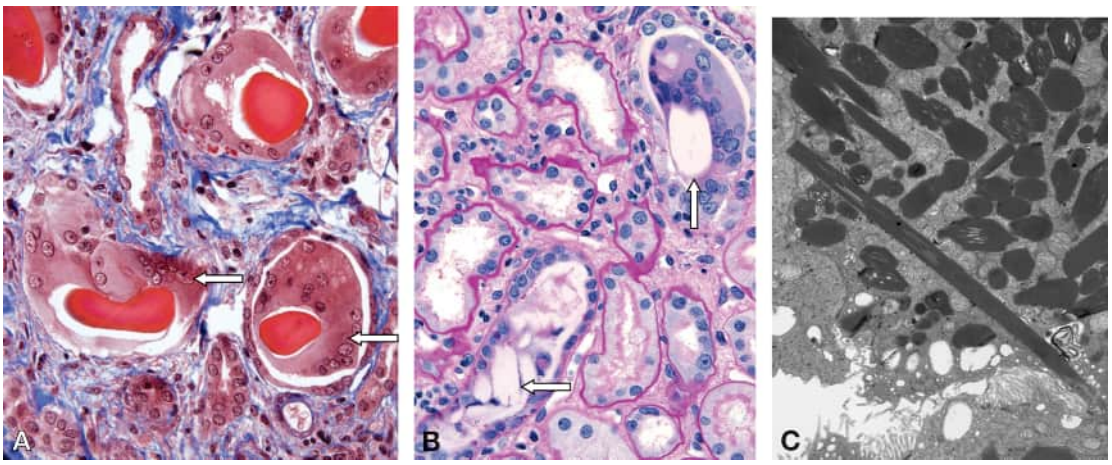


FIGURE 7.12 Light-chain lesions by light microscopy. A, B. Light-chain (Bence Jones) cast nephropathy. A. Orange light-chain casts with adjacent and engulfing multinucleated giant cells (arrows) (Masson trichrome ×400). B. Periodic acid-Schiff (PAS)-negative light-chain casts (arrows), the upper right cast is surrounded by a giant cell (PAS ×400). C. Crystalline tubulopathy. Light-chain depositing as electron-dense crystals in tubular cells (×7,500).

LM: LC casts, which are angulated, fractured, or coarsely granular staining orange on Masson trichrome and periodic acid-Schiff (PAS) negative preferentially in distal tubules.

Casts are often surrounded or engulfed by multinucleated giant cells. The number of casts in cortical tubules in predictive of outcome. Crystalline inclusions may also stain as light blue on hematoxylin and eosin (H&E).
IF: Casts stain strongly for the abnormal LC with minimal staining for other immune reactants.

Management of LC cast nephropathy

- Clone-directed therapy for paraproteinemia
- PLEX is not recommended.
- Supportive care: IV fluid as needed, avoid nephrotoxins.

Direct deposition/processing of paraproteins in kidney tissues

Monoclonal Ig deposition (of LC or HC) disease (MIDD) (Figure 7.13)

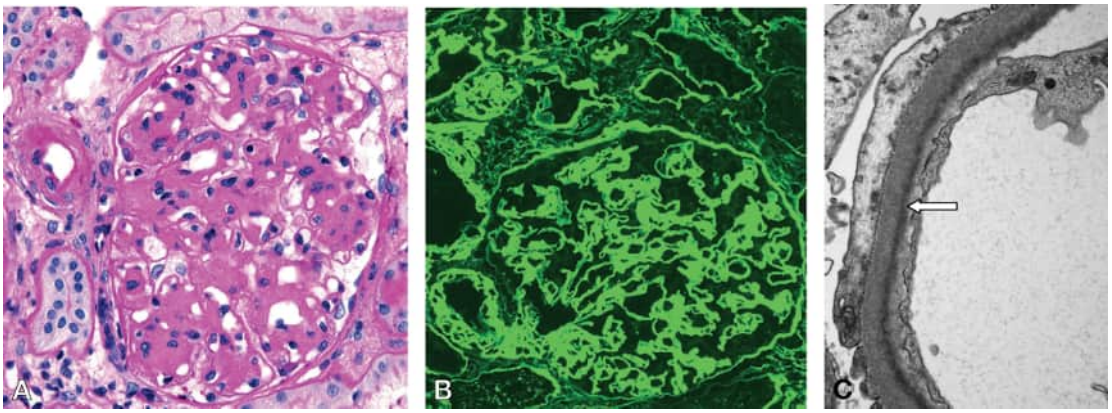


FIGURE 7.13 **Monoclonal immunoglobulin deposition disease.** A. Thickened and somewhat nodular mesangial regions; this may mimic nodular diabetic glomerulosclerosis (periodic acid-Schiff ×400). B. Strong linear κ light-chain staining of all basement membrane and extracellular material (×300). C. Dark granular electron-dense material (arrow) along the glomerular capillary basement membrane; it also involves tubular basement membranes (×19,000).

- LC and/or HC may deposit into different kidney structures (eg, tubular basement membrane, GBM, or interstitium). Based on the type of Ig chain deposition, MIDD can be categorized as follows:
  - Light-chain deposition disease (LCDD) (80%)
  - Heavy-chain deposition disease (HCDD) (10%)
  - Light- and heavy-chain deposition disease (LHCDD) (10%)
- Clinical significance/manifestations of MIDD:
  - Most MIDD are due to monoclonal κ-LC deposition (two-thirds of cases).
  - MIDD does not present with proteinuria mismatch because GBM is affected and significant albuminuria can occur.
  - The amount of abnormal monoclonal protein in the serum or urine may be low due to extensive tissue deposition.

- In MIDD, the deposits of LC or HC have not been processed into amyloid fibrils, thus are Congo red negative.

Amyloidosis

- LCs are partially metabolized in macrophages, then secreted. The metabolized fragments may precipitate into granular deposits and/or β-pleated fibrils as "amyloid," which is Congo red positive.
- The incidence of amyloid light chain (AL) amyloidosis is approximately 20% to 30% of patients with MM.
- Approximately two-thirds of cases are from λ LCs and one-third from κ LC.
- Clinical manifestations:
  - GBM and mesangial amyloid deposition can manifest as albuminuria and even nephrotic range proteinuria. Since routine urinalysis with a dipstick can detect albuminuria well, "proteinuria mismatch" is not characteristic of renal amyloidosis, in contrast to that seen in myeloma kidney/cast nephropathy.
  - In the case of predominant interstitial and vascular involvement, progressive kidney injury occurs but typically with minimal proteinuria.
- Treatment should target reducing the synthesis of the amyloid protein. Various approaches have been used, including steroids, alkylating agents, proteasome inhibitors, and autologous stem cell transplantation. Measurement of FLC and κ/λ ratio are useful response markers. Untreated patients with MM-associated AL amyloidosis have a median survival of less than a year, with cardiac involvement a major determinant.
- Histopathology (**Figure 7.14**):

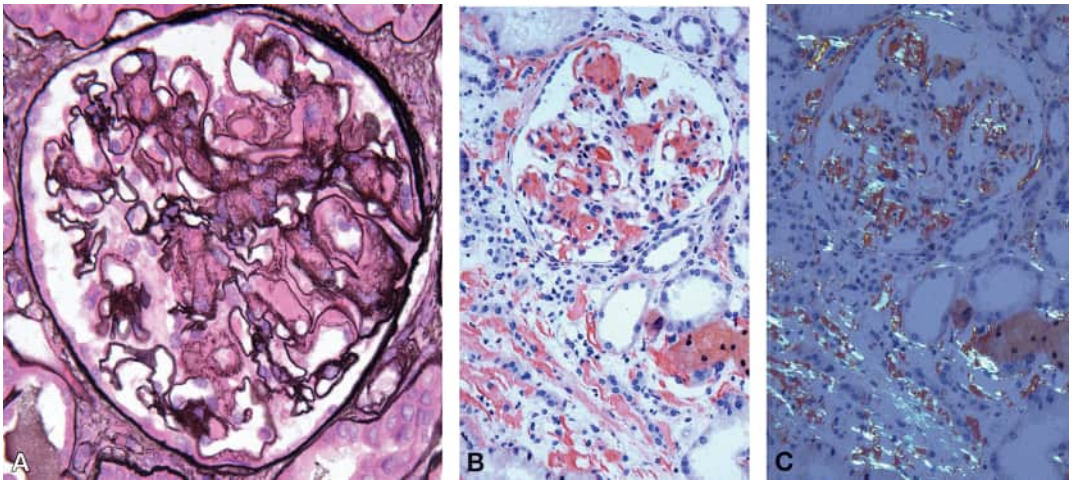


FIGURE 7.14 **Amyloidosis.** A. Silver-negative material in mesangial regions and capillary walls (Jones silver ×400). B. Positive Congo red stain in glomerular and interstitial amyloid (×200). C. Polarized Congo red stain showing apple green birefringence in the amyloid (×200).

  - **LM:** Amyloid stains as silver and PAS-negative material in mesangial regions and/or capillary walls. It is Congo red positive and displays apple green birefringence when viewed with polarized light.

- **IF:** smudgy amorphous staining for the appropriate LC and/or HC. If it is a non-AL (amyloid A [AA], transthyretin, Lect2, fibrinogen Aα), there is no LC or Ig staining.
- **EM:** 10 nm haphazardly arranged fibrils

Crystal-storing histiocytosis

- Rare condition due to accumulation of LC crystals in histiocytes localized in renal interstitium, mesangium, or within glomerular loops
- Crystal-storing histiocytosis has been reported in MM and B-cell lymphoproliferative disorders.

Kidney manifestations due to reactive inflammatory response

A combination of the following lesions may be present in the same patient.

Tubulointerstitial nephritis

- May occur in plasma cell disorders including MM
- Associated with FLC deposition in tubular basement membrane and lysosomes of tubular epithelial cells

Glomerular disease

Glomerular diseases reported with paraproteinemia include MPGN pattern of injury, monoclonal cryoglobulinemia, PGNMID, intraglomerular IgM deposits with resultant thrombus formation (Waldenström macroglobulinemia), C3G, immunotactoid GN, FSGS, and, rarely, MCD.

NOTE

An MPGN pattern associated with monoclonal gammopathy often presents with both IgG and C3 deposits, or less commonly, IgM and C3 deposits. Rarely, some monoclonal Ig proteins and/or their fragments can inhibit complement alternative pathway regulatory proteins (CfH or C3Bb) and induce a "complement-only" form of GN appearing as C3G. Older patients with C3G should be evaluated for a monoclonal gammopathy.

- PGNMID presents similarly to IC-MPGN in terms of both clinical manifestations and histopathology. The major difference is, in PGNMID, there is positive staining for a *monoclonal* Ig on IF microscopy (ie, single LC isotope and single HC subtype, typically IgG3 κ).
- C3G may be seen in patients with monoclonal gammopathy.
  - Underlying etiology: Dysregulation of the complement alternative pathway by the monoclonal Ig acting as an autoantibody has been suggested.
  - Monoclonal gammopathy should be evaluated as an underlying etiology of C3G in patients older than 50 years of age.
- Immunotactoid glomerulopathy is a rare condition associated with monoclonal gammopathy in up to 67% of cases, with approximately 50% having a clone in the CLL lineage.
- PGNMID and immunotactoid GN may present with hypocomplementemia in one-third of cases.

Other systemic complications related to paraproteins

Plasma cell infiltration
Interstitial infiltration of malignant cells causing kidney injury: malignant B cells (ie, CLL or monoclonal B-cell lymphoproliferative disorders) and rarely malignant plasma cells
Rhabdomyolysis may occur due to LC deposition in muscles.
Hyperviscosity syndrome:

- Associated with excessive formation of abnormal polymers of IgM (Waldenström), IgA or IgG3, or κ-LCs
- Clinical manifestations: blurred vision, neurologic symptoms, confusion, oral/nasal bleeding, heart failure, kidney injury/acute tubular necrosis (ATN)
- Treatment: plasmapheresis if obvious symptoms regardless of serum viscosity index. Serum viscosity index may not correlate well with symptoms.

Thrombotic microangiopathy
TMA has been reported in some patients with monoclonal gammopathy, including MM, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance (MGUS). The underlying pathogenesis is thought to be complement mediated.

Electrolyte abnormalities

Hypercalcemia (especially MM): nephrocalcinosis, interstitial nephritis, reduced renal perfusion due to hypercalcemia-induced vasoconstriction, intratubular calcium salt precipitation
Hyperuricemia: acute uric acid nephropathy (typically with uric acid level >15 mg/dL), interstitial nephritis
Volume depletion:

- Hypercalcemia-induced nephrogenic diabetes insipidus
- Reduced oral intake
- Cardiomyopathy (eg, amyloid involvement)

Chemotherapy-induced kidney injury

- Lenalidomide: acute interstitial nephritis, Fanconi syndrome
- Proteasome inhibitors (eg, bortezomib, carfilzomib, ixazomib) are rarely associated with TMA.
- Carfilzomib may also be associated with tumor lysis–like syndrome and ATN.

Other diagnostic study/treatment-related causes of kidney injury

- Drugs (NSAIDs), antibiotics
- Use of IV contrast dye with CT
- Bisphosphonates (zoledronate: ATN; pamidronate, zoledronate: collapsing FSGS)

Diagnosis of Paraprotein-Related Disorders

Urine studies

Characteristics suggesting cast nephropathy:

- Urine FLC 1,500 mg/L or more with concurrent low urinary albumin excretion
- Fanconi syndrome: euglycemic glucosuria, phosphaturia, RTA
- 24-Hour urine protein electrophoresis and immunofixation with a predominance of monoclonal LCs
- Proteinuria mismatch suggests the presence of FLC (a.k.a. Bence Jones protein).
  - Urine dipsticks readily detect urine albumin, but not FLC, which is the protein that makes up the "cast" nephropathy. However, total urine protein measured as uPCR or 24-hour urine collection can detect and measure all forms of proteins, including FLC. Thus, in the presence of FLC, uPCR and 24-hour urine protein may be much greater than that measured on routine dipstick protein.
  - Proteinuria mismatch may be unmasked by the addition of sulfosalicylic acid (SSA) to the urine sample because SSA precipitates all proteins including all albumin and FLC.

Characteristics suggesting glomerular process:
High-level albuminuria or nephrotic range proteinuria suggests direct injury to GBM: amyloidosis (most commonly AL amyloidosis), MIDD, immunotactoid glomerulopathy, monoclonal cryoglobulinemic GN (IgM), PGNMID, or C3G.

Serum metabolic panel

- Low to positive serum anion gap
- Hypercalcemia (especially MM)
- Pseudohyperphosphatemia: High serum FLC levels may give falsely high readings of phosphate levels by some automated analyzers.
- High serum total protein-to-albumin ratio
- Low complements may be present in PGNMID and immunotactoid GN.

Testing options for monoclonal gammopathy

- Serum protein electrophoresis with immunofixation
- 24-Hour urine protein electrophoresis
- Serum FLC (serum κ and λ LC quantification)

See **Appendix A7.5** for details on monoclonal gammopathy testing.

Kidney biopsy

- Kidney biopsy may be done if unknown underlying etiology.
- Kidney biopsy is not typically done if urine studies overwhelmingly support the diagnosis of cast nephropathy or AL amyloidosis is already diagnosed in tissues other than kidneys.

Management

Supportive therapy

- Volume repletion with crystalloids as needed

- Dialysis support as necessary
- Plasmapheresis in the presence of hyperviscosity

Management of hypercalcemia

- Administer normal saline as tolerated.
- GC with or without bisphosphonates (first-line pamidronate; second-line zoledronate due to dosing concerns with low GFR for the latter; calcitonin if refractory to bisphosphonates or rapid calcium reduction is needed)
- Hemodialysis for severe hypercalcemia (ie, serum calcium level >18 mg/dL)

Direct treatment of paraproteinemia/MM

Autologous hematopoietic cell transplantation (HCT)

- HCT provides superior progression-free survival and is the key component in treating MM in eligible patients.
- Patients with one or more of the following are not considered eligible for autologous HCT: age older than 77 years, frank cirrhosis of the liver, poor functional status unless due to bone pain, and NYHA functional status class III or IV

Chemotherapy

- Reduction of serum FLC with chemotherapy predicts renal response in MM.
- Choice of therapy depends on disease characteristics and comorbidities, patient/provider preference, and feasibility. Acceptable regimens include:
  - Lenalidomide plus dexamethasone-based regimen with or without daratumumab or bortezomib or both. Lenalidomide is an analog of thalidomide that inhibits tumor angiogenesis, cytokine release, and proliferation.
    - Daratumumab, bortezomib, *lenalidomide, and dexamethasone* (DVRd)
    - Bortezomib, *lenalidomide, and dexamethasone* (VRd)
    - Daratumumab, *lenalidomide, and dexamethasone* (DRd)—consider for patients who cannot tolerate bortezomib (ie, those with preexisting neuropathy).
    - *Lenalidomide plus dexamethasone* may be considered for frail adults who cannot tolerate more aggressive therapy.
  - Lenalidomide-free regimen: Bortezomib, CYC, and dexamethasone may be considered in patients at higher risk of complications with lenalidomide (eg, patients with AKI, increased thromboembolic risks).

Amyloidosis, Fibrillary Disorders, and Cryoglobulinemia

Non-AL amyloidosis

- In addition to AL amyloidosis seen in MM, there are many other proteins that have been identified in amyloid deposits in the kidneys.
- When amyloid-containing tissue fails to show AL, immunohistochemical, IF, or mass spectrometry testing should be performed to identify other types of amyloid, including

AA protein, LECT2, lysozyme, the apolipoproteins (including A1 and A2), fibrinogen, gelsolin, and transthyretin.

- AA amyloid is the most common secondary form of amyloid, associated with chronic infections (tuberculosis being one of the most common causes outside North America), as well as chronic inflammatory diseases (familial Mediterranean fever, rheumatoid arthritis).
- LECT2 amyloid is almost as frequent as AA amyloid, particularly in patients of Hispanic or Middle Eastern ethnicity.

Nonamyloid fibrillary disorders

Fibrillary GN

- A very rare proliferative form of GN associated with the presence of the protein DnaJ heat shock protein family member B9 (DNAJB9). Fibrillary GN is not associated with monoclonal gammopathy and thought to be a distinct unrelated condition from immunotactoid GN.
- Histopathology:
  - **EM:** randomly oriented fibrillar deposits with a mean diameter of 20 nm
  - **IF:** deposits staining for DNAJB9, IgG, C3, and κ and λ LCs
- Clinical manifestations:
  - GN with active urinary sediment and typically RPGN
  - Kidney prognosis is poor. ESKD may be reached within 2 to 6 years.
  - Disease recurrence following kidney transplant is thought to be high.
- Treatment is not well established. Likely supportive with or without RTX or CYC.

Others

- Fibronectin GN: autosomal dominant disorder associated with massive deposition of fibronectin
- Collagenofibrotic (collagen III) GN: GN associated with massive accumulation of atypical type III collagen fibrils in mesangium and subendothelial space
- Nail-patella syndrome and hereditary multiple exostoses syndrome (or hereditary multiple osteochondromas syndrome) with NS and associated glomerular fibrillar collagen deposition

Cryoglobulinemia: cryoglobulinemic GN

Cryoglobulinemic vasculitis with renal involvement (cryoglobulinemic GN) refers to an inflammatory syndrome that affects small to medium vessels due to the precipitation of cryoglobulin-containing ICs. Cryoglobulins are Igs that precipitate at cold temperatures (<37°C) and redissolve with warming.

Cryoglobulinemia can be classified into three categories:

- Type I:
  - The cryoglobulins are monoclonal, typically IgG or IgM, and less commonly IgA or FLC.

- The monoclonal Igs arise from a monoclonal gammopathy such as MM, Waldenström macroglobulinemia, CLL, or MGUS.
- Typical manifestations: digital ischemia, purpura, livedo reticularis due to vascular occlusion from cryoprecipitate. Symptoms are dictated by cold ambient temperatures.

- Type II:
  - The cryoglobulins are composed of a mixture of a monoclonal Ig, typically IgM (but can also be IgG or IgA) with rheumatoid factor plus polyclonal Igs.
  - Type II may be associated with viral infections such as hepatitis C (and less commonly hepatitis B, HIV), autoimmune diseases (SLE, Sjögren disease), or lymphoproliferative disorders.
  - Typical manifestations: fatigue, arthralgias, myalgias, palpable purpura, peripheral neuropathy; symptoms are not dependent on ambient temperature as seen in type I.
- Type III:
  - The cryoglobulins are composed of a mixture of polyclonal IgM plus polyclonal IgG.
  - Type III can be associated with viral infections and autoimmune disorders.
  - Typical manifestations: similar as type II

Diagnostic evaluation

- Viral infections: HIV, hepatitis B and C, Epstein-Barr virus
- Autoimmune disease: ANA, ANCA, acute phase reactants, C3, C4, CH50, rheumatoid factor
- Monoclonal gammopathy: cryoglobulin titers, serum and urine protein electrophoresis and immunofixation, serum FLC

Management and prognosis depend on the underlying etiology.

Table 7.14 summarizes amyloidosis, fibrillary disorders, and cryoglobulinemia. **Figure 7.15** shows amyloid fibrils (smallest with diameter 10-12 nm), fibrillary fibrils (15-25 nm), immunotactoid microtubules (30-50 nm), and cryoglobulin microtubules (20-30 nm).

Table 7.14 Summary of key clinical and morphologic features of amyloidosis, fibrillary disorders, and cryoglobulinemia

	Amyloidosis	Fibrillary GN	Immunotactoid GN	Cryoglobulinemia
Clinical associations	• Primary AL predominantly due to monoclonal Ig light-chain fragments • Secondary AA due to chronic inflammatory disease (eg, familial Mediterranean fever, chronic infections) • Others: LECT2, lysozyme,	• Rare proliferative GN associated with the presence of DNAJB9 • Fibrillary GN is not associated with monoclonal gammopathy and thought to be a distinct unrelated condition from	• Rare condition associated with monoclonal gammopathy in up to 60%-70% of cases • Approximately half of these cases have a clone in the CLL lineage.	• Viral infections (eg, HIV, hepatitis B and C, Epstein-Barr virus) • Autoimmune diseases • Monoclonal gammopathy

	Amyloidosis	Fibrillary GN	Immunotactoid GN	Cryoglobulinemia
	apolipoproteins A1 and A2, fibrinogen, gelsolin, transthyretin	immunotactoid GN.		
Congo red stain	Positive (see **Figure 7.14**)	Negative	Negative	Negative
EM	Haphazardly arranged 10 nm fibrils	Randomly arranged 15-25 nm fibrils	Parallel arrays of 35-50 nm microtubules	Randomly arranged to clusters of 20-30 nm curved microtubules
IF	Depends on underlying etiology	Deposits staining for DNAJB9, IgG, C3, and κ and λ light chains	Monoclonal deposition with a restricted light chain, either κ or λ	Depends on underlying etiology
LM	Nodular or diffuse PAS- and silver-negative deposits of amorphous materials in mesangial matrix (may resemble matrix Kimmelstiel-Wilson nodules) and basement membranes of capillary loops and tubules, arteriolar walls, interstitium	Focal mesangial or diffuse proliferative, MPGN pattern, or MN	Similar to fibrillary GN: Focal mesangial or diffuse proliferative, MPGN pattern, or MN	Depends on underlying etiology, usually segmental PAS-positive capillary thrombi, may be many endocapillary monocytes

Abbreviations: CLL, chronic lymphocytic leukemia; DNAJB9, DnaJ heat shock protein family member B9; EM, electron microscopy; GN, glomerulonephritis; HIV, human immunodeficiency virus; IF, immunofluorescence; LM, light microscopy; MPGN, membranoproliferative glomerulonephritis; PAS, Periodic-acid Schiff.

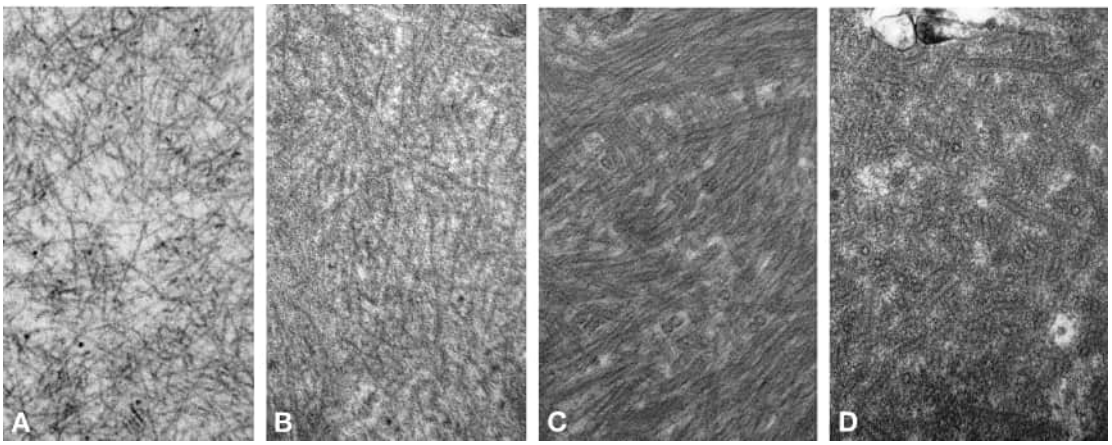


FIGURE 7.15 **Fibrillary deposits.** A. Amyloid. Haphazardly arranged 10 nm fibrils. B. Fibrillary glomerulonephritis. Randomly arranged 15 to 25 nm fibrils. C. Immunotactoid glomerulonephritis. Parallel arrays of 35 to 50 nm microtubules, often monoclonal. D. Cryoglobulin. Randomly arranged to clusters of 20 to 30 nm curved microtubules (All ×72,000).

ALPORT SYNDROME

Background and Epidemiology

- Mutations involving the α3, α4, and α5 chains of collagen type IV (COLA4α3, COL4α4, COL4α5) make up a spectrum of glomerular nephropathies that include the "classic Alport syndrome", "thin basement membrane nephropathy (TBMN)", familial benign hematuria, and other nonsyndromic conditions.
- Increasingly, mutations of the COLA4 α3, α4, or α5 chains have been identified in patients with morphologic FSGS whose clinical and/or biopsy manifestations did not clearly classify them as either primary or secondary FSGS.
- The prevalence of Alport syndrome varies from 1 per 5,000 to 1 per 50,000 live births in the United States and Europe. Prevalence varies further according to location and whether pathogenicity of specific genotypic variants is validated by in vivo experiments versus in silico extrapolations, the latter being more subject to potential misclassification.

Pathogenesis

Background: There are six genetically distinct collagen type IV chains (α1, α2, α3, α4, α5, α6) that form three triple helical protomers [α1,α1,α2], [α3,α4,α5], and [α5,α5,α6], where

- [α1,α1,α2] protomer is present in all basement membranes.
- [α**3,**α**4,**α**5**] protomer is present in **kidney**, lung, testis, cochlea, and eye.
- **[**α**5,**α**5**,α6] protomer is present in **skin**, smooth muscle, esophagus, and **kidney**.
- COL4**A1** and COL4**A2** at 13q34 encode α1 and α2, respectively.
- COL4A3 and COL4A4 at 2q35-37 encode α3 and α4, respectively.
- COL4A5 and COL4A6 on chromosome X encode α5 and α6, respectively.
- Mutations of α5 and α6 chains are transmitted as expected for X-linked genes.

Disease states:

- Mutations affecting any of the α3, α4, or α5(IV) chains alter the type IV collagen triple helical complex and impair the organizational structure of the GBM collagen network, leading to glomerulosclerosis.
- In patients with autosomal recessive Alport syndrome, primary mutations in the α3(IV) or α4(IV) chains prevent the assembly of the type IV collagen triple helix and incorporation into the GBM.
- Large deletion or nonsense mutations cause more severe disease than missense mutations.

NOTE

In most patients with X-linked α5(IV) mutations, the α3, α4, and α5(IV) chains undergo proteasomal degradation and are all absent from the GBM despite continuing transcription of the α3(IV) and α4(IV) genes. The GBM is characterized by the absence of the α3, α4, and α5(IV) chains and replacement by the solitary contribution of endothelial type IV collagen α1 and α2(IV) chains.

Classification of Alport Syndrome and Related Disorders Based on Genetic Inheritance:

X-linked (80%-85%) mutations involve the *COL4A5* gene, which codes the α5(IV) chain.

- More women are affected with X-linked Alport than men because women can get the disease from either the mother or father, but men can only inherit the disease from the mother.
- Female heterozygous carriers: Almost all have hematuria but with variable outcome. Only a minority develop ESKD presumably due to "lyonization," a process whereby only one X chromosome is active per cell. Thus, in most women with X-linked Alport, approximately half of the cells express the mutant gene, while the other half express the normal gene. These patients may present with TBMN.

Autosomal recessive (10%-15%) mutations involve either *COL4A3* or *COL4A4* genes encoding the α3(IV) chain (which contains the Goodpasture antigen) or α4(IV) chain, respectively:

- Females are as severely affected as males.
- Clinical manifestations in both sexes are identical to males with classic X-linked Alport.

Autosomal dominant (<5%) with heterozygous mutations in either *COL4A3* or *COL4A4* genes:

- Include patients diagnosed as thin basement membrane nephropathy and benign familial hematuria.
- Some patients may present with similar clinical and pathologic features as those of X-linked disease but with slower kidney function decline

Digenic mutations. The presence of two pathogenic variants (eg, COL4A3 and COL4A4 or COL4A5 and COL4A3 or COL4A4) in different type IV collagen genes (digenic) has also been reported in some families.

Additive inheritance. While some heterozygous mutations in the *COL4A3* or *COL4A4* genes cause autosomal dominant Alport syndrome and progressive kidney failure, others only develop TBMN, a typically more benign condition where patients present with microscopic hematuria without progression to ESKD. Genetic factors other than mutations in these collagen genes have been suggested to affect phenotypes, with a clinical disease spectrum from benign to ESKD.

De novo mutations of the α3-5(IV) chains may also occur.

Clinical Manifestations

Renal manifestations of Alport syndrome:

- Asymptomatic persistent microscopic or gross hematuria
- Boys without hematuria by age 10 unlikely to have X-linked Alport syndrome.

- In X-linked females, recurrent gross hematuria, proteinuria, high-frequency hearing loss, and diffuse GBM thickening are associated with worse kidney outcomes.
- ESKD:
  - X-linked or autosomal recessive disease: ESKD usually occurs by age 35 but may be later in life.
  - Autosomal dominant: ESKD occurs later in life (ie, age 45-60).

Extrarenal manifestations of Alport syndrome

Sensorineural hearing loss:

- Thought to be due to impaired adhesion of auditory sensory cells to the inner ear basilar membrane lacking the normal α3-4-5(IV) collagen network
- Initial hearing loss is in high-frequency range.
- Rate of hearing loss is similar to the rate of kidney disease progression.

Ocular abnormalities:

- Anterior lenticonus with thinning of lens capsule due to abnormal α3, α4, and α5(IV)
- Other ocular findings: spherophakia, anterior polar and posterior cortical cataract, corneal changes with recurrent corneal erosions
- Retinal findings: drusen, perifoveal dot and fleck retinopathy, neovascularization

Leiomyomas:

- May be associated with X-linked Alport but are rare
- Affected patients carry deletions that involve COL4A5 extending into the adjacent *COL4A6* gene. Deletions involving both COL4A5 and COL4A6 are thought to cause misregulation of neighboring genes and resultant smooth muscle overgrowth.

Arterial aneurysms have been reported in young males and may involve thoracic, abdominal aorta, and even intracranial arteries.

Histopathology

LM: interstitial foamy macrophages in the absence of significant proteinuria or NS. Global and/or segmental glomerulosclerosis may be present in more advanced disease.

EM:

- Classic Alport: GBM with irregular thinning and thickening, layered or lamellated "basket-weave" appearance in the thickened area due to GBM injury and remodeling, and subepithelial scalloping. There are no electron-dense deposits (**Figure 7.16**).
- In TBMN, the GBM width may be only one-third that of normal GBM (**Figure 7.17**).

NOTE

Histopathologic finding of TBMN does not necessarily rule out classic Alport syndrome due to the possibility of inadequate biopsy or early Alport. Clinical evaluations for hearing loss and abnormal optical lens, investigation for family history, and follow-up visits are necessary to rule out Alport syndrome. Genetic analysis may help define the specific Alport entity, eg, classic Alport syndrome, TBMN, or hematuric Alport kidney disease.

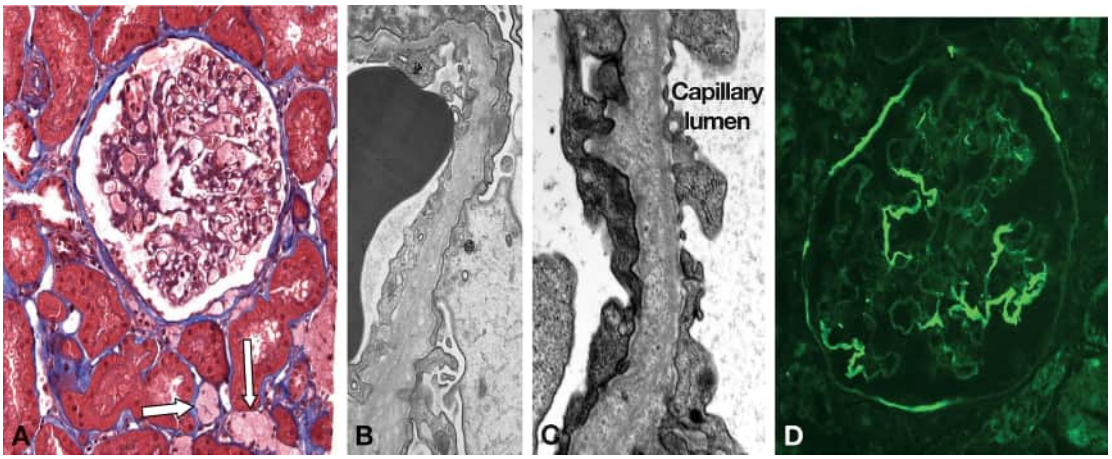


FIGURE 7.16 **Alport syndrome.** A. Normal glomerulus and interstitial foam cells (arrows) (Masson trichrome ×200). B. Irregular thick and thin layered glomerular capillary basement membrane (×19,000). C. Thick glomerular capillary basement membrane with "basket-woven" appearance and subepithelial scalloping (×25,000). D. Focal Bowman capsular and glomerular capillary basement membrane staining for α5(IV) collagen chain in a female heterozygote for X-linked Alport syndrome (×400).

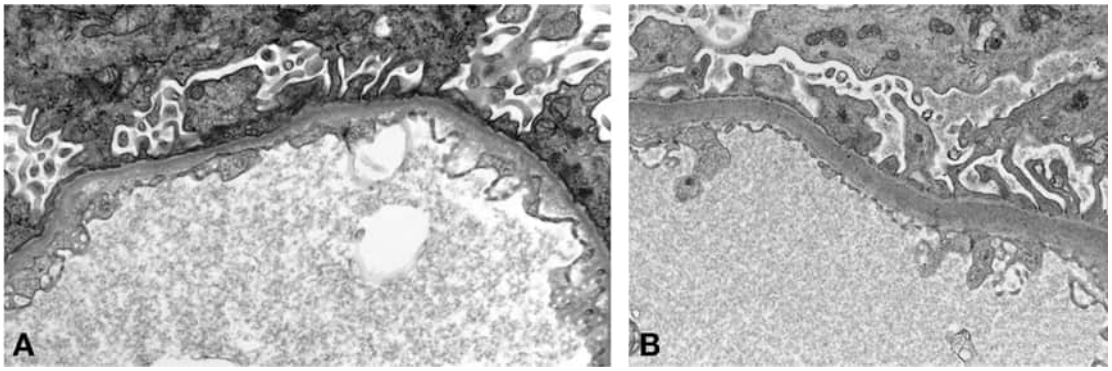


FIGURE 7.17 **Thin basement membrane nephropathy.** A. Thin glomerular capillary basement membrane, measuring 107 to 125 nm in width. Note there is no subepithelial scalloping or layering/lamellation of the basement membrane and the podocyte foot processes are partially effaced. B. Normal glomerular capillary basement membrane measuring 320 nm for comparison (original magnifications ×12,000).

IF: Pattern of staining depends on chain being stained for and type of mutation.

- Staining for the α3(IV) or α5(IV) chain will be positive within the normal GBM since the protomers [α3,α4,α5] are distributed within the GBM.
- In an X-linked Alport male, that is mutation of the α5(IV) chain, staining for α3,4 and 5(IV) chains are typically negative due to the lack of [α3,α4,α5] protomer formation.
- In an X-linked Alport female, that is mutation of the α5(IV) chain, IF staining for α3,4, and 5(IV) is segmental due to lyonization.
- In an autosomal recessive Alport:
  - No α3(IV)-α5(IV) labeling may be detected in the GBM, but α5(IV) from the [α5,α5,α6] protomer will be positive in Bowman capsule and basement membrane of collecting ducts.
  - Staining for α5(IV) in the skin will be normal because the skin protomer is [α5,α5,α6]. Mutations involving α3 or α4 do not affect the expression of skin

[α5,α5,α6] protomer.

Diagnosis

Clinical syndrome, particularly if known family history
Kidney or skin biopsy

- Kidney biopsy: Note that classic lamellation of GBM may not be present in early disease.
- Skin biopsy can be stained for α5(IV) chain.
  - Absent or segmental staining suggests X-linked Alport.
  - Normal staining may signify:
    - Autosomal recessive or dominant Alport syndrome involving the α3 or α4(IV) chain
    - Mutation of α5(IV) that affects the function but not structure of the chain
    - Diseases other than Alport

Genetic testing (See Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington; 1993-2024.)

- This is the gold standard for diagnosis. Mutations in COL4A3, COL4A4, and/or COL4A5 may be present. Inheritance may be X linked (COL4A5) or may be autosomal recessive or autosomal dominant (COL4A3, COL4A5). Mutations may be nonsense, missense, or truncating or may involve large deletions or frameshifts. Patients with missense mutations may have milder disease manifestations.
- Genetic counseling is advised for patients with COL4 mutations.
- The Alport Syndrome Classification Working Group proposed that a diagnosis of Alport syndrome should be conferred in any individual in whom a type IV collagen variant is thought to be causative for the phenotypic traits of Alport syndrome, irrespective of the number of either symptoms or organ involvement.

Management

- Standard supportive management: ACEi or ARB to reduce proteinuria and rate of disease progression
- SGLT2i, aminoglycoside analogs, endothelin receptor type A antagonists, lipid transport–modifying drugs, HC, bardoxolone methyl, and gene replacement therapies are currently under investigation as treatment.

Kidney transplantation

- Recurrent disease does not occur in the transplanted allograft because the donor kidney has normal GBM.
- Anti-GBM disease occurs in 3% to 4% of affected males who receive transplants. X-linked females do not develop post-transplant anti-GBM disease because they generally do carry a normal copy of the affected gene and do express the normal counterpart.
- In males with X-linked disease, antibodies are directed primarily against the α5(IV) chain, but antibodies against the α3(IV) chain are also found in some patients.

- In patients with autosomal recessive Alport syndrome who develop post-transplant anti-GBM disease, the predominant target of anti-GBM antibodies is the α3(IV) chain.
- Kidney donors who are heterozygous for the pathogenic *COL4A3* or *COLA44* gene may experience worsening of proteinuria and/or kidney function after donation.
- There is a high risk of recurrence in patients with Alport syndrome who lose a first allograft to post-transplant anti-GBM disease.

THROMBOTIC MICROANGIOPATHY / HEMOLYTIC-UREMIC SYNDROME

Background

TMAs are clinical syndromes characterized by:

- Thrombocytopenia with platelet counts less than 150,000/μL or more than 25% decline in platelet count from baseline,
- Microangiopathic hemolytic anemia (MAHA), and
- End-organ dysfunction involving one or more organs (eg, brain, kidneys, GI tract)

Pathologic features

Artery, arteriolar and glomerular capillary wall thickening, intraluminal thrombi, endothelial cell swelling, and various degrees of luminal narrowing or obstruction

Clinical Disorders Associated With TMA

TMA may be seen in various clinical disorders:

Shiga toxin–mediated HUS (a.k.a. diarrhea-associated HUS)
Complement-mediated TMA (previously known as aHUS). Historically, the term aHUS was used to distinguish it from Shiga toxin–mediated HUS. However, such term does not reflect a specific cause.
Thrombotic thrombocytopenic purpura (TTP)
Pregnancy-associated TMA syndromes (hemolysis, elevated liver enzymes, and low platelets [HELLP], TTP, complement-mediated TMA)
TMA associated with other clinical disorders: disseminated intravascular coagulation (DIC), systemic infections, drugs, cobalamin C deficiency, malignancies, autoimmune disease such as SLE, scleroderma, and APS

Shiga toxin–mediated HUS (diarrhea-associated HUS)

Clinical manifestation: HUS usually occurs 5 to 10 days after the onset of a bloody diarrhea.
Pathogenesis: caused by Shiga toxin–producing enterohemorrhagic *E. coli* strains. Most common etiologic agent: *E. coli* O157:H7. Other: *E. coli* O104:H4 (large HUS outbreak in Germany in 2011). Toxin-mediated endothelial cell damage leads to thrombotic occlusion of arteriole and glomerular capillary, endothelial cell swelling, apoptosis of glomerular and tubular cells, often with extensive cortical necrosis.
Therapy:

- Mainly supportive
- Plasmapheresis may be considered in patients with severe AKI or neurologic involvement.
- AVOID: heparin and antithrombotic agents (increased bleeding risk), antimotility (may prolong the persistence of *E. coli* in the intestinal lumen), antibiotics (may increase HUS risk presumably due to acute release of large amount of preformed toxins from lysed bacteria)

Long-term outcomes:
Death or ESKD in 12%, long-term CKD in 25%
CNS involvement and AKI requiring dialysis at presentation portend worse prognosis.

Complement-mediated TMA (aka aHUS)

Sporadic accounts for most cases, familial in less than 20% of cases.
Clinical manifestations: A preceding infection, which can be viral and may include diarrheal illness, may occur in 80% of children and 50% of adult patients. Patients may present with severe hemolytic anemia, thrombocytopenia, AKI, CNS and GI bleeding, cardiac ischemic events, and pulmonary hemorrhage and hypoxemia.
Pathogenesis: dysregulated activation of the alternative complement pathway due to genetic mutations of or autoantibody formation against various complement-regulatory proteins. Genetic abnormalities found in approximately 60% of patients and may include:

- Loss-of-function mutations of CFH, CFI, CD46 (previously known as membrane cofactor protein or MCP), or thrombomodulin (*THBD*). THBD is an endothelial surface anticoagulant protein that also modulates complement on cell surfaces. Cells that express *THBD* variants inactivate C3b less efficiently.
- Gain-of-function mutations of C3 or CFB
- Formation of CFH inhibitory antibodies
- Combination of gene mutations (eg, *CFH/CFHR* hybrid genes)
- Diacylglycerol kinase ξ (*DGKE*) gene mutation associated with infantile recessive aHUS

Potential triggering factors: pregnancy (usually postpartum), gastroenteritis, upper respiratory infection, other infections, organ transplantation, and malignant HTN
Therapy:

- Eculizumab, a humanized anti-C5 monoclonal antibody, should be first-line therapy.
- If eculizumab is unavailable, initiate PLEX.
- GC may have added beneficial effect in patients with CFH autoantibodies.
- Ravulizumab is a humanized anti-C5 monoclonal antibody engineered from eculizumab to prolong the drug half-life. It was approved by the FDA for use in aHUS in December 2018. NOTE: Eculizumab is not effective in DGKE-mediated aHUS unless the patient has concomitant complement abnormalities.
- Other therapies: Combined liver-kidney transplantation is a therapeutic option for patients with CFH mutations. It corrects the genetic complement defect and prevents CFH-associated HUS recurrence post-transplant. Perioperative plasma infusion/exchange and eculizumab recommended. Disadvantage: 20% mortality risk. Ongoing clinical trial: Factor B inhibitor (eg, Iptacopan).

Thrombotic thrombocytopenic Purpura (TTP)

Background: ADAMTS13 is a protease that normally cleaves ultra-large von Willebrand factor (vWF) multimers on endothelial cell surface into smaller fragments to make them "less sticky" to circulating platelets. The absence of normally functioning ADAMTS13 leads to the presence of ultra-large vWF multimers, increased platelet trapping, and subsequent intravascular formation of microthrombi.

Clinical manifestations: Classic pentad for TTP (thrombocytopenia, MAHA, kidney failure, neurologic signs, fever) is rare.

Pathogenesis and therapy:

- *Acquired TTP*: severe functional deficiency of ADAMTS13 due to the presence of ADAMTS13 inhibitory autoantibodies (ADAMTS13 activity <5%-10%)
  - PLEX should be initiated pending ADAMTS13 activity test results. Plasma replaces reduced protease activity. PLEX, as compared with plasma infusion alone, may offer the additional advantage of removing any potential ADAMTS13 antibodies. (The risk of TTP may be predicted using PLASMIC score [Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem cell or solid organ transplant, MCV, INR, Creatinine] pending ADAMTS13 activity test results.)
  - Adjunctive GC therapy may have added benefits in patients with autoimmune forms of TTP by inhibiting the production of anti-ADAMTS13 autoantibodies.
  - RTX, an anti-CD20 monoclonal antibody, should be considered in refractory or relapsing immune-mediated ADAMTS13 deficiency.
  - RTX has also been used to prevent relapses in patients with autoantibodies.
  - Caplacizumab is a monoclonal antibody fragment (nanobody) that binds to vWF**,** thereby inhibiting platelet adhesion and microvascular thrombosis. Caplacizumab does not affect the production of anti-ADAMTS13 autoantibodies. Caplacizumab was FDA approved in 2019 for use in acquired TTP in conjunction with PLEX and IST.
- *Genetic TTP*: deficiency of ADAMTS13 due to homozygous or compound heterozygous ADAMTS13 gene mutation
  - Plasma therapy replaces ADAMTS13. Relapse is common.
  - PLEX is often required during acute episodes.

NOTE

Shiga toxin–mediated HUS and TTP may have significant overlapping clinical signs and symptoms at presentation (eg, thrombocytopenia, increased serum LDH, schistocytes on peripheral smear, CNS involvement, and diarrheal illness. 20% to 60% of patients with TTP have kidney failure). Diagnosis for the distinct syndrome may not be obvious at presentation and requires testing for ADAMTS13 activity. Immediate PLEX initiation is recommended if TTP is suspected pending ADAMTS13 result. Eculizumab should be initiated when there is a high index of suspicion for complement-mediated TMA. **Figure 7.18** summarizes the diagnostic criteria, clinical manifestations, pathogenesis, and therapy of Shiga toxin–mediated HUS, complement-mediated TMA, and TTP.

FYI

PLASMIC score

- The PLASMIC score may be used to predict the likelihood of having TTP in patients who present with thrombocytopenia (platelets <150) and evidence of MAHA (ie, schistocytes on peripheral smear).
- PLASMIC score relies on Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem cell or solid organ transplant, MCV, INR, Creatinine.
- +1 point is given for each of the following if present:
  - Platelet count less than 30×10^9/L, +1
  - Evidence of hemolysis (reticulocyte count >2.5%, undetectable haptoglobin, or indirect bilirubin >2.0 mg/dL [34.2 µmol/L]), +1
  - Absence of active cancer, +1
  - Absence of stem cell or solid organ transplant, +1
  - Mean corpuscular volume (MCV) less than 9.0×10^{-14} L (<90 fL), +1
  - INR less than 1.5, +1
  - SCr less than 2 mg/dL (176.8 µmol/L), +1
- Risk of having severe ADAMTS13 deficiency (ie, activity level <15%)
  - Score 0 to 4: 0% (low risk)
  - Score 5: 6% (intermediate risk)
  - Score greater than 5: 72% (high risk)

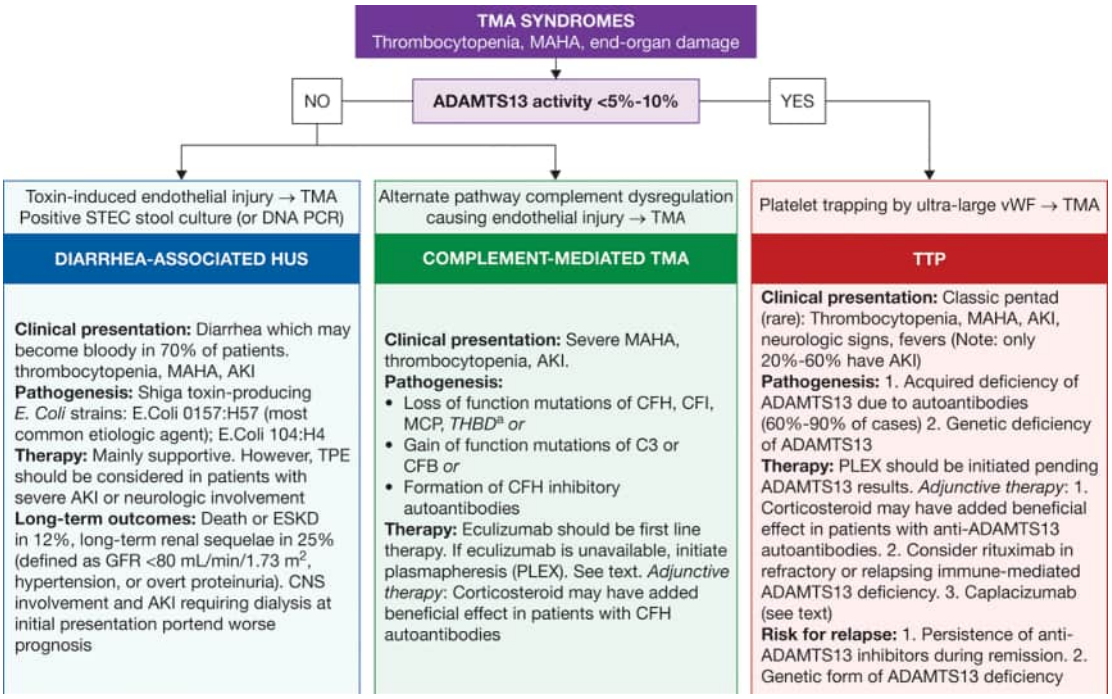

TMA SYNDROMES
Thrombocytopenia, MAHA, end-organ damage
NO
ADAMTS13 activity <5%-10%
YES
Toxin-induced endothelial injury → TMA
Positive STEC stool culture (or DNA PCR)
DIARRHEA-ASSOCIATED HUS
Clinical presentation: Diarrhea which may become bloody in 70% of patients. thrombocytopenia, MAHA, AKI
Pathogenesis: Shiga toxin-producing E. Coli strains: E.Coli 0157:H57 (most common etiologic agent); E.Coli 104:H4
Therapy: Mainly supportive. However, TPE should be considered in patients with severe AKI or neurologic involvement
Long-term outcomes: Death or ESKD in 12%, long-term renal sequelae in 25% (defined as GFR <80 mL/min/1.73 m2, hypertension, or overt proteinuria). CNS involvement and AKI requiring dialysis at initial presentation portend worse prognosis
Alternate pathway complement dysregulation causing endothelial injury → TMA
COMPLEMENT-MEDIATED TMA
Clinical presentation: Severe MAHA, thrombocytopenia, AKI.
Pathogenesis:
• Loss of function mutations of CFH, CFI, MCP, THBD[a] or
• Gain of function mutations of C3 or CFB or
• Formation of CFH inhibitory autoantibodies
Therapy: Eculizumab should be first line therapy. If eculizumab is unavailable, initiate plasmapheresis (PLEX). See text. Adjunctive therapy: Corticosteroid may have added beneficial effect in patients with CFH autoantibodies
Platelet trapping by ultra-large vWF → TMA
TTP
Clinical presentation: Classic pentad (rare): Thrombocytopenia, MAHA, AKI, neurologic signs, fevers (Note: only 20%-60% have AKI)
Pathogenesis: 1. Acquired deficiency of ADAMTS13 due to autoantibodies (60%-90% of cases) 2. Genetic deficiency of ADAMTS13
Therapy: PLEX should be initiated pending ADAMTS13 results. Adjunctive therapy: 1. Corticosteroid may have added beneficial effect in patients with anti-ADAMTS13 autoantibodies. 2. Consider rituximab in refractory or relapsing immune-mediated ADAMTS13 deficiency. 3. Caplacizumab (see text)
Risk for relapse: 1. Persistence of anti-ADAMTS13 inhibitors during remission. 2. Genetic form of ADAMTS13 deficiency

FIGURE 7.18 Differential diagnoses of the primary forms of TMA.
Abbreviations: AKI, acute kidney injury; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; CNS, central nervous system; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; MAHA, microangiopathic hemolytic anemia; MCP, membrane cofactor protein; PCR, polymerase chain reaction; PLEX, plasma exchange; STEC, Shiga toxin–producing enterohemorrhagic *E. coli*; THBD, thrombomodulin; TMA, thrombotic microangiopathy.

[a]Cells expressing *THBD* gene variant inactivate C3b less efficiently.

Pregnancy-associated TMA syndromes

Pregnancy-associated TTP due to ADAMTS13 deficiency:

- May occur early in pregnancy, but typically occurs in the late second and third trimesters, with a median gestational age of 23 weeks

- During pregnancy, plasma vWF including the ultra-large multimers increases steadily up to 20% to 500% of normal at term, while ADAMTS13 activity declines gradually from the end of the first trimester to the end of early puerperium. The opposite changes in vWF and ADAMTS13 levels may lead to greater risk of TTP precipitation in at-risk individuals.

Pregnancy-associated complement-mediated TMA:

- Pathogenesis: underlying maternal complement dysregulation; infection is thought to be a potential triggering factor.
- Clinical manifestations:
  - Typically occurs postpartum (80%) but may occur early in pregnancy
  - Late (ie, postpartum) occurrence is thought to be due to the loss of placental protective complement inhibitory factors against mother's underlying complement dysregulation.
  - Pregnancy-associated complement-mediated TMA is associated with a higher incidence of fetal losses (4.6% vs 2%-3%) and preeclampsia (7.4% vs 4%-5%) compared to the general population.
  - Two-thirds of affected patients develop ESKD within a month of diagnosis.

Severe preeclampsia associated with HELLP syndrome

- HELLP diagnostic criteria defined by the American College of Obstetricians and Gynecologists:
  - MAHA
  - LDH 600 IU/L or more
  - Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to more than twice the upper limit of normal
  - Platelet count less than 100,000 cells/μL
- HELLP diagnostic criteria defined by Tennessee Classification System: MAHA manifested by at least two of the following:
  - Peripheral smear with schistocytes and burr cells
  - Serum bilirubin 1.2 mg/dL or more
  - Low serum haptoglobin (≤25 mg/dL) or LDH 2 times or above the upper limit of normal
  - Severe anemia unrelated to blood loss (defined as hemoglobin [Hb] <8-10 g/dL, depending on trimester)
  - Elevated AST and ALT to 2 times or above the upper limit of normal
  - Platelet count less than 100,000 cells/μL

TMA associated with other clinical disorders

Disseminated intravascular coagulation (DIC)

- Associated with sepsis, liver failure, malignancy, tissue death, obstetric complications such as preeclampsia, septic abortion

- Classic presentation: elevated prothrombin time/partial thromboplastin time (PT/PTT), increased fibrinogen degradation product (FDP), increased D-dimer
- Low-grade or chronic DIC: PT/PTT and fibrinogen may be normal, but MAHA will be present and FDP and D-dimer will be increased.

NOTE

While Shiga toxin–mediated HUS, TTP, and complement-mediated TMA have normal plasminogen and fibrinogen turnover, DIC has increased fibrinolysis and plasminogen activator. Unlike DIC where PT/PTT are typically elevated, these levels are normal in HUS and TTP.

Infections: HIV, CMV, parvovirus, *Streptococcus pneumoniae*
Drugs: ticlopidine (off market), quinine (off market), clopidogrel, valacyclovir, oral contraceptives, several chemotherapeutic agents, mitomycin C, cyclosporine, tacrolimus, sirolimus, everolimus
Other causes of TMA: autoimmune disease such as SLE or APS (discussed below), systemic sclerosis, malignant HTN, stem cell transplant, cobalamin C deficiency (due to methylmalonic aciduria and homocystinuria type C mutations)

Systemic Lupus Erythematosus – Thrombotic Thrombocytopenic Purpura (SLE-TTP)

Epidemiology

- TTP typically precedes the diagnosis of SLE in children. 6% of patients with TTP have SLE.
- SLE typically precedes the diagnosis of TTP in adults. Less than 5% of patients with SLE have TTP.
- Differential diagnoses of MAHA other than TTP in patients with SLE:
  - DIC
  - Malignant HTN
  - Catastrophic APS (multiple organ thromboses)
  - Active lupus complicated by hemolytic anemia
  - Vascular immune complex deposition
  - Small-vessel vasculitis with end-organ damage

Clinical manifestations

- Presence of MAHA, anemia, thrombocytopenia
- Patients with SLE-associated TTP tend to be younger males, have worse kidney function (both proteinuria and SCr), class IV diffuse proliferative LN, lower C3 levels, and other complications such as APS, serositis, pulmonary HTN, nephritis, and CNS involvement.
- Mortality in SLE-associated TTP is approximately 50% and is commonly associated with infections.

Diagnosis

- Diagnosis is based on clinical assessment, serologic and coagulation tests, and exclusion of all other differential diagnoses above.
- Unclear utility of ADAMTS13 in SLE: Reduced ADAMTS13 levels and/or presence of ADAMTS13 antibodies may be detected in patients with SLE *without* overt TMA. However, patients with SLE with TTP do have severely depressed ADAMTS levels or high titers of anti-ADAMTS13 antibodies.

Management

- Poor data
- PLEX plus IST (eg, corticosteroids and CYC) to control both TTP and active SLE, respectively. Anticoagulation should be added if APS nephropathy is present. APS nephropathy is discussed in a later section.
- RTX may be considered if above fails. Rationale for RTX use: Anti-endothelial antibodies, antiplatelet antibodies, and anti-ADAMTS13 antibodies have been reported in patients with SLE-TTP, implicating an autoimmune mechanism in the pathogenesis of SLE-TTP.

SLE and Thrombosis

General risks

- Leukopenia has been reported to be associated with a decreased risk of both arterial and venous thromboembolic events.
- The coexistence of the 3 aPLs (lupus anticoagulant, anticardiolipin, and anti–β2-glycoprotein I) is especially high risk for thromboembolic events.
- The use of antimalarials (HC) is protective against both arterial and venous thromboembolic events.
- The use of aspirin is inconclusive but warranted due to its low adverse effect profile.
- Routine evaluation for other genetic conditions must also be considered (eg, factor V Leiden, methylenetetrahydrofolate reductase, fibrinogen γ mutations).

Risks for arterial thromboembolic events

- Patients with SLE with arterial thromboembolic events are at increased risks for MI and stroke after adjustments for traditional risk factors.
- Reported risks for arterial thromboembolic events:
  - Traditional factors: age, male, gender, smoking, dyslipidemia, HTN, obesity, hyperhomocysteinemia
  - Nontraditional factors: SLE disease duration, presence of aPLs, higher SLE damage scores, duration and cumulative dose of corticosteroid use

Risks for venous thromboembolic events

Reported risks for venous thromboembolic events: male gender, higher body mass index, aPLs, low serum high-density lipoprotein (HDL), hemolytic anemia, kidney disease

Antiphospholipid Syndrome (APS)

Systemic APS

Systemic APS may be classified as primary or secondary APS. Primary APS has no associated systemic disease, whereas secondary APS is associated with a systemic disease (eg, autoimmune diseases such as SLE, rheumatic diseases), certain infections, and medications.

Definition of APS:

Systemic APS is defined as the presence of one or more of the following clinical manifestations *and* one or more of the following laboratory criteria (Sapporo/Sydney classification criteria):

Clinical manifestations:

- Imaging or histologic evidence of venous, arterial, or small-vessel thrombosis in any tissue or organ (eg, deep vein thrombosis, pulmonary embolism, strokes, MI, renal artery or vein thrombosis)
- One unexplained death of a morphologically normal fetus at 10 weeks or more of gestation, *or* one or more premature birth of a morphologically normal neonate before 34 weeks of gestation because of eclampsia, preeclampsia, or placental insufficiency, *or* three or more consecutive spontaneous pregnancy losses at less than 10 weeks of gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes

Laboratory criteria: positive aPLs detected on two or more occasions 12 weeks or more apart. aPLs are autoantibodies directed against plasma proteins bound to anionic surfaces. aPLs are typically IgG or IgM but can be IgA.

- aPLs of interest: lupus anticoagulant, anticardiolipin antibodies, and anti–β2-glycoprotein I. Lupus anticoagulant is thought to carry the highest risk for thrombosis and has been reported to be the primary predictor of adverse pregnancy outcome in patients with aPLs.
- The prevalence of aPLs is 1% to 5% of general population but as high as 16% to 40% in patients with SLE, and 16% in those with rheumatoid arthritis.
- The prevalence of APS may be more than 20% during long-term follow-up in patients with SLE.

Kidney disease in primary APS

Primary APS may cause renal artery or vein thrombosis, cortical ischemia/necrosis, hematuria, tubulointerstitial fibrosis, glomerular lesions (eg, MN, MCD, FSGS, pauci-immune GN), or APS nephropathy.

Antiphospholipid-associated nephropathy

- This is a vaso-occlusive kidney injury due to TMA.
- Up to one-third of patients with APS nephropathy do not have systemic APS.
- Histopathology of APS nephropathy (**Figure 7.19**):

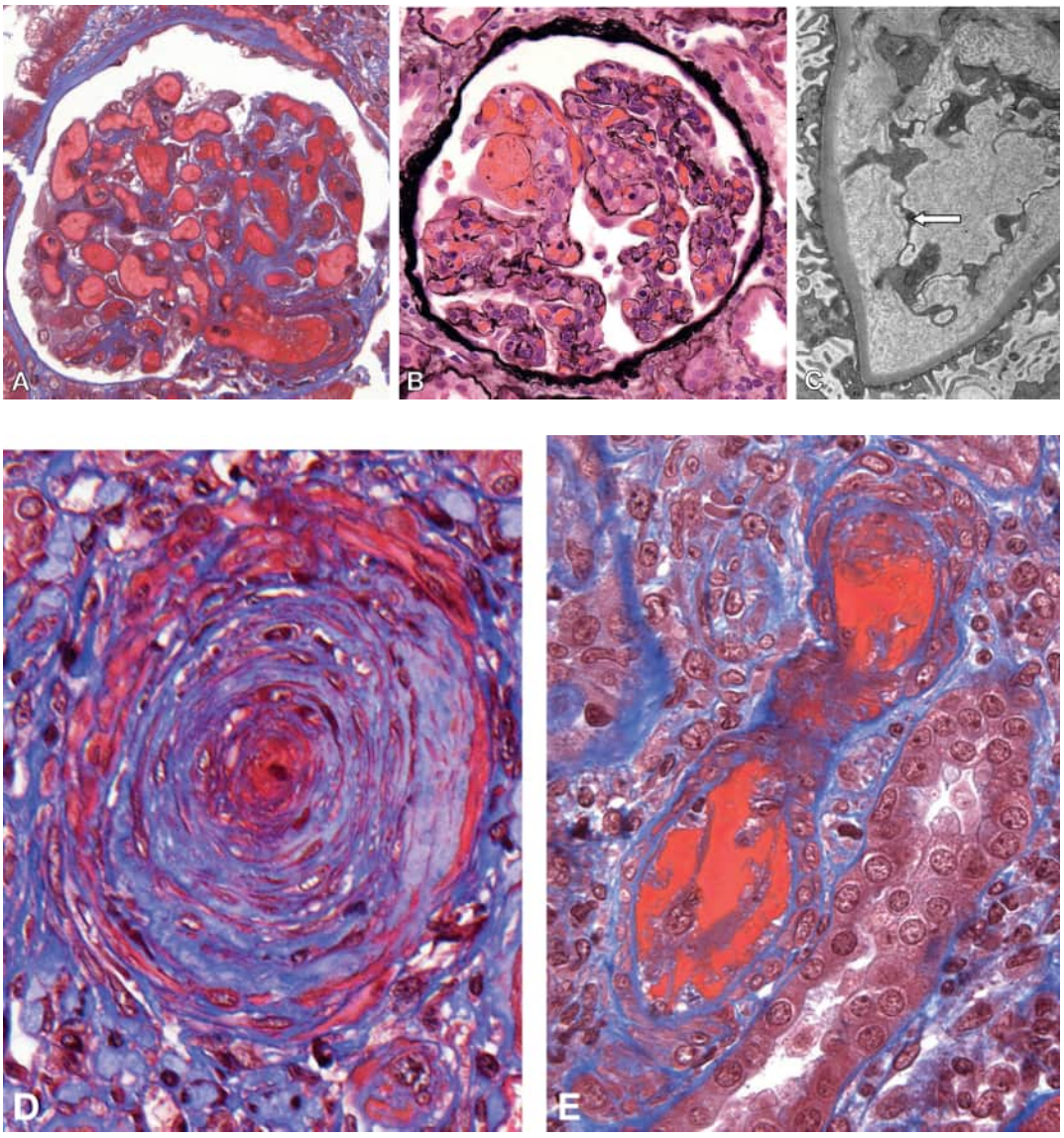


FIGURE 7.19 **Antiphospholipid syndrome.** A. Bland thrombosis of arteriole and glomerular capillaries (Masson trichrome ×400). B. Glomerular capillary thrombosis with irregular, ischemically wrinkled capillary walls and segmental capillary wall double contours (Jones silver ×400). C. Wide subendothelial lucency (arrow) (which stains for fibrin) corresponding to thickened capillaries on light microscopy (×14,000). D. Arteriole with "onion skin" appearance due to muscular hypertrophy, with a thrombus in the very narrowed lumen (Masson trichrome ×600). E. Thrombosed arteriole (Masson trichrome ×400). Arterial/arteriolar fibrin thrombi with or without fibrin extending into the vascular intima and endothelial cell swelling with narrowed lumens.

- **LM:**
  - Arterial/arteriolar fibrin thrombi with or without fibrin extending into the vascular intima, endothelial cell swelling, and luminal narrowing
  - Fragmented RBCs in vessel lumens or walls, or in areas of glomerular mesangiolysis
  - Concentric thickening (onion skinning + mucoid subendothelial widening) of arterial/arteriolar walls

    - Glomerular thrombosis, mesangiolysis, ischemic wrinkling sometimes with capillary wall double contours
- **IF:** fibrin in glomerular capillaries and/or vessel walls and/or lumens
- **EM:** subendothelial electron lucent widening between glomerular capillary basement membrane and swollen endothelium; may be red cell fragments

Pathogenesis of APS

The inciting event is thought to arise from aPL-mediated blood vessel injury, followed by endothelial disruption, formation of β2-glycoprotein I IC, and activation of the classic complement pathway activating endothelial cells, platelets, and circulating monocytes, all leading to a thrombogenic state.

Management of APS

- Lifetime anticoagulation for APS, even APS nephropathy alone
- Warfarin with goal INR 2.0 to 3.5. INR greater than 3.0 may be associated with anticoagulant-related nephropathy (ARN refers to AKI associated with glomerular hemorrhage and intratubular RBC obstruction). Underlying CKD is thought to be a risk factor for ARN (**Figure 7.20**).

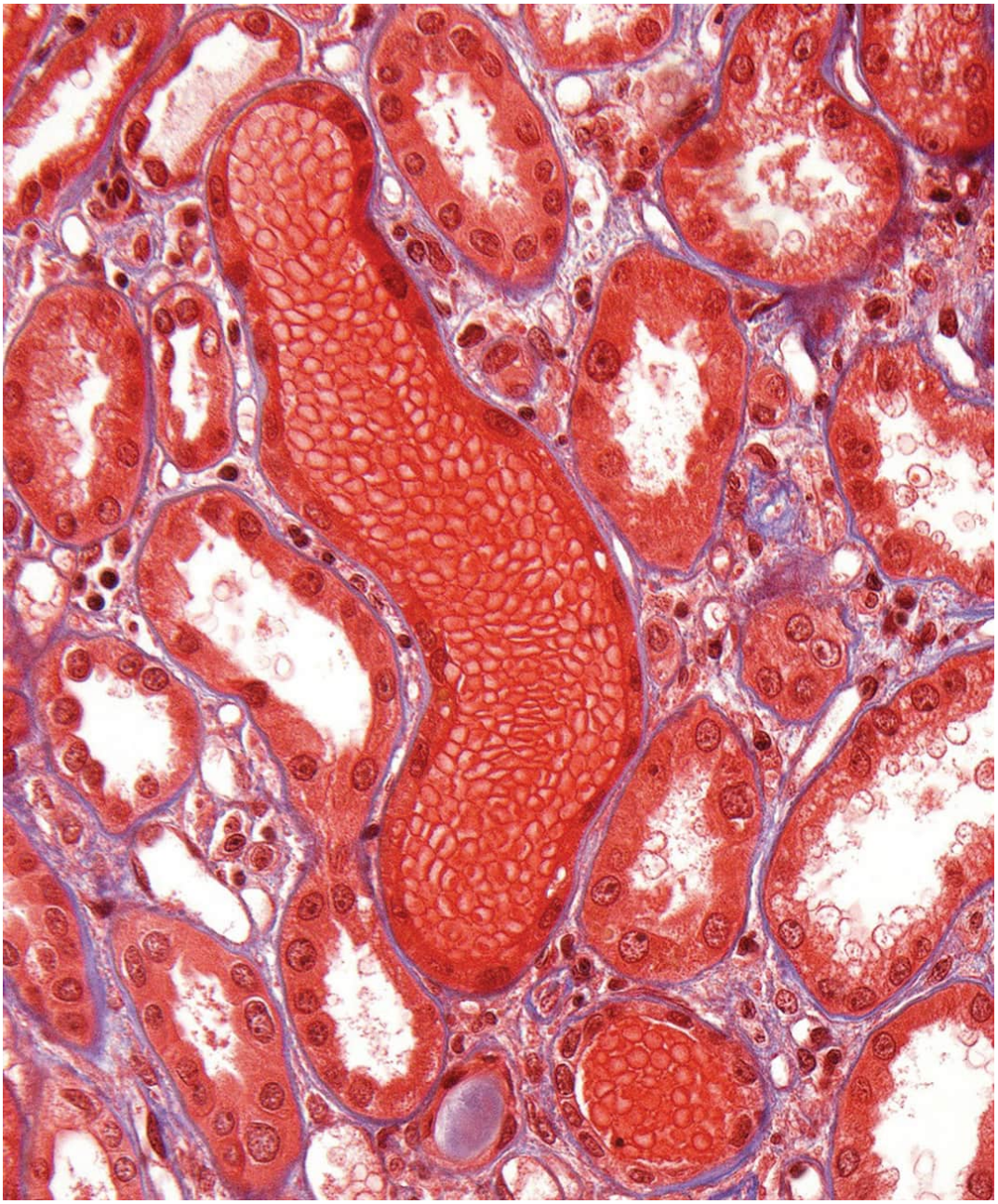


FIGURE 7.20 **Anticoagulant-related nephropathy.** Red blood cells are within and occluding the lumen of distal tubules (Masson trichrome ×400).

- Direct-acting oral anticoagulants (DOACs)
  - Meta-analysis showed similar venous thrombosis rates in DOAC or warfarin-treated patients, but higher arterial thrombosis rates with DOAC compared with warfarin-treated patients.
  - For most patients with APS, anticoagulation with warfarin is recommended over DOAC unless poor adherence to follow-up of coagulation studies or warfarin intolerance is a problem.
- LMWH is the treatment of choice for pregnancy complicated by APS. Its use may also alleviate symptoms of migraine headache.

- HC can be beneficial in patients with APS without evidence of SLE.

Management of APS during pregnancy

- Routine screening for aPLs is recommended among patients with SLE.
- Adverse outcomes of APS and positive aPLs: late fetal loss (after 10 weeks of gestation), increased relative risk of preeclampsia
- Women with APS and arterial thrombotic events are at increased risk for stroke, and maternal morbidity and mortality.
- For women with aPLs but not meeting clinical criteria for APS, pregnancy morbidity risk is unknown.

Anticoagulation:

- For women with known APS receiving chronic anticoagulation: Convert warfarin to LMWH during pregnancy.
- For women with no known history of thrombotic events, but with obstetric criteria for APS of having either three or more pregnancy losses or late pregnancy loss, prophylactic anticoagulation consisting of a low-dose aspirin with either unfractionated heparin or LMWH should be initiated.
- For patients with aPLs not meeting APS criteria, low-dose aspirin before or as soon as pregnancy is recognized is suggested.

DIABETIC KIDNEY DISEASE (DKD)

Epidemiology

- DKD is the most common primary diagnosis for patients who start dialysis (~50%).
- Kidney diseases in patients with diabetes who present with ESKD:
  - 60%: classic DKD (large kidneys, proteinuria >1 g/d, and/or diabetic retinopathy [DR])
  - 25% to 30%: another primary kidney disease in addition to DKD
  - 10% to 15%: atypical presentation with ischemic nephropathy (low-level proteinuria)
- Cumulative prevalence of proteinuria is approximately 50% to 60% at 25 years after diagnosis of diabetes.
- Cumulative prevalence of progression to ESKD is approximately 60% at 5 years after onset of proteinuria. Progression to ESKD is more common among Black, Native American, and Hispanic ethnic minorities in the United States.
- Cumulative prevalence of proteinuria and progression to ESKD are substantially greater for patients with type 2 diabetes mellitus (T2D) than type 1 diabetes mellitus (T1DM).

Risks for the Development of DKD and Progression

Unmodifiable risks:

- Genetic susceptibility: likely multigenic. No single gene with a large effect has been identified.
- Ethnicity: Blacks, Hispanics, Pima Indians with T2D
- Gender: Caucasian males and African American females
- Age: possibly early onset
- Duration of DM

Modifiable risks: HTN, early glomerular hyperfiltration, prolonged uncontrolled hyperglycemia, obesity, tobacco smoking, use of oral contraceptives, high-protein diet

Clinical Manifestations

Albuminuria:

- A moderate increase in albuminuria is a biomarker for eventual DKD.
- The American Diabetes Association recommends screening for microalbuminuria in:
  - All patients with T2D at the time of diagnosis and annually thereafter
  - All patients with T1DM 5 years after the diagnosis and annually thereafter
- Of note, 10% to 25% of patients with T2D and reduced kidney function have little or no proteinuria despite having biopsy-proven diabetic nephropathy.

(Microscopic) Hematuria:

- May occur with DKD
- Even RBC casts have been reported rarely in biopsy-proven DKD, but other glomerular diseases MUST be ruled out

Morbidities and mortality:

- Increasing albuminuria and decreasing GFR correlate with CVE and renal events in patients with T2D.
- Mortality among patients with diabetes with ESKD is 1.5- to 2.0-fold greater compared to those without diabetes.

Natural History

Proposed scheme of DKD stages for T1DM (less reliable for DKD in T2D)

Pre-DKD (0-5 years since disease onset): glomerular hyperfiltration, renal hypertrophy

Incipient DKD (5-15 years)

- Microalbuminuria (30-300 mg/24 hours or overnight albuminuria at 20-200 µg/min in at least two of three consecutive nonketotic sterile urine samples) occurs in 20% to 30% of patients, less than 50% of whom will progress to overt nephropathy, HTN.
- Structural changes: mesangial expansion, moderate glomerular basement thickening, arteriolar hyalinosis

Overt DKD (15-25 years)

- Proteinuria (>300 mg albuminuria/24 hours or overnight albuminuria >200 µg/min—when severe albuminuria occurs, the majority will progress to ESKD), NS, reduced glomerular filtration
- Structural changes: severe GBM thickening, often mesangial matrix nodules (Kimmelstiel-Wilson lesions), tubulointerstitial fibrosis

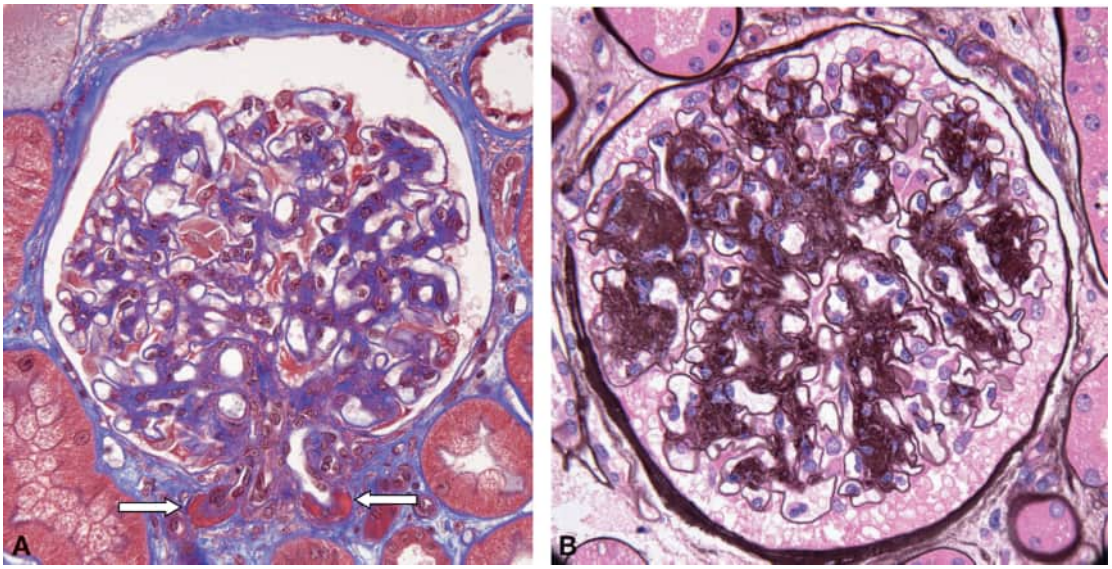
ESKD (>25 years): 4% to 17% at 20 years from the time of diagnosis

Reflecting tight glycemic control shown to be of benefit in the DCCT trial, coupled to a "legacy effect" of early tight glycemic control, the incidence of ESKD as a consequence of T1DM has been falling for decades and is estimated to be approximately 8% after 30 years of follow-up.

Pathogenesis

For interested readers, refer to **Appendix A7.9** for underlying biochemical changes and pathogenesis of DKD.

Structural Changes and Histopathology (Figure 7.21)



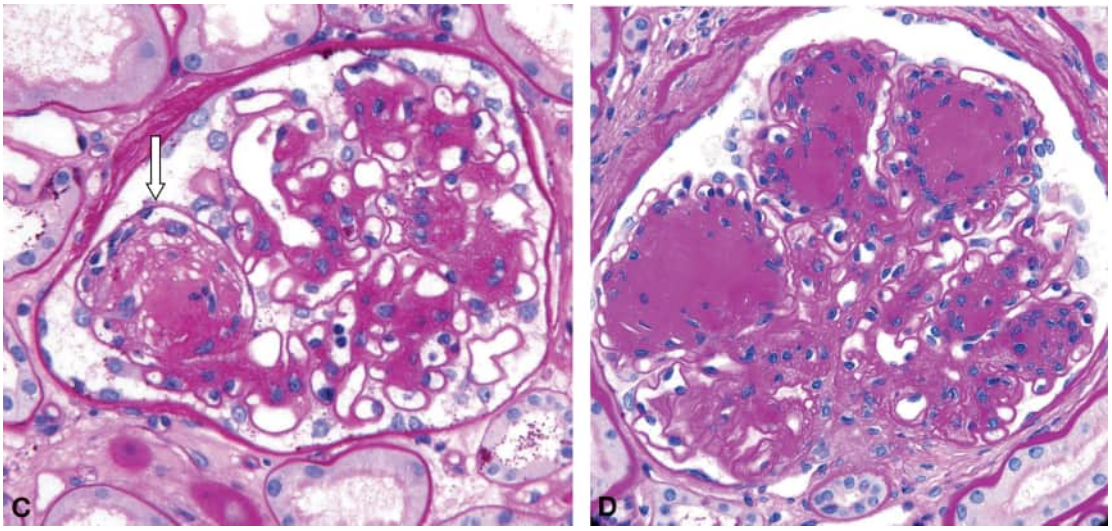


FIGURE 7.21 **Diabetic nephropathy.** A. Mild/early diffuse diabetic glomerulosclerosis with mild expansion of matrix. Note hyalinization of afferent and efferent arterioles (arrows). (Masson trichrome ×400). B. Moderate diffuse increase in mesangial matrix (Jones silver ×400). C. Diffuse and nodular matrix expansion with mesangiolysis and microaneurysm formation (arrow) (periodic acid-Schiff ×400). D. Global mesangial matrix nodules with peripheral nuclei (periodic acid-Schiff ×400).

Kidney weight increases by approximately 15% due to glomerular hypertrophy and hyperfiltration.

Histopathology

Early glomerular hypertrophy

GBM thickening (may be 5× normal)

Mesangial matrix expansion

- Due, in part, to hyperglycemia-induced increased matrix production or glycation of matrix proteins, advanced glycation end product (AGE) crosslinking with collagen, and decreased matrix degradation
- Mild-to-severe diffuse mesangial expansion without nodules

Nodular mesangial matrix expansion (Kimmelstiel-Wilson lesion)

- Associated with mesangiolysis and capillary microaneurysms
- Differential diagnoses of nodular glomerulosclerosis: dysproteinemias (eg, amyloidosis and MIDDs, and immunotactoid GN), fibronectin glomerulopathy, collagen III glomerulopathy, chronic hypoxic/ischemic conditions including smoking-related glomerulopathy, chronic MPGN, metabolic syndrome, or idiopathic
- Patients with matrix nodules are more likely to have DR and worse kidney function.

Vascular lesions:

- Hyalinization of both afferent and efferent arterioles is pathognomonic for diabetic nephropathy.
- Arterial intimal fibrosis

Advanced diabetic sclerosis

Indications for Kidney Biopsy in Patients With DM

- Absence of DR (particularly in T1DM). Note that the absence of DR in T2D does not exclude DKD.
  - DR is present in only approximately 50% to 65% of patients with T2D and DKD. Although the absence of DR does not exclude DKD, patients without DR have a higher likelihood of having a nondiabetic glomerular disease.
  - Patients with T1DM and DKD *almost always* have other evidence of diabetic microvascular disease (ie, DR, neuropathy), but the converse is not true (ie, not all patients with DR have DKD).
- Acute onset of proteinuria, particularly if less than 5 years from diagnosis in T1DM
- Presence of active urinary sediment (eg, RBC casts) or significant hematuria (gross hematuria)
- Rapid decline in kidney function
- Presence of extrarenal manifestations and/or positive serologies suggestive of another glomerular disease (eg, positive ANCA, hypocomplementemia)

Management

DKD management should focus on healthy living (optimal weight, exercise, smoking cessation) and optimal BP, lipid, and glycemic control.

Glycemic control

- Maintain hemoglobin A1C (HbA1c) approximately 7% for both T1DM and T2D.
- For patients with diabetes with severe end-organ complications, an HbA1c approximately 7.5% is acceptable.
- In patients with long-standing DM and known cardiovascular disease (CVD), available data do not support strict glycemic control in reducing risk for further CVD events or mortality (see **Appendix A7.10** for clinical data).

Protective effects of intensive glycemic control

- Reduction in rates of development of microalbuminuria
- Partial reversal of glomerular hypertrophy and hyperfiltration
- Stabilization or decrease protein excretion in patients with albuminuria after apparent normoglycemia greater than 2 years
- Slowing of GFR decline
- Successful pancreas transplantation leads to stabilization of glomerular structure at 5-year follow-up *and* significant reversal of DKD histopathologic changes at 10 years.

Specifics about noninsulin therapy in patients with T2D

- In patients with T2D and established atherosclerotic cardiovascular disease (ASCVD), multiple ASCVD risk factors, or DKD, the use of an SGLT2i with demonstrated CV

benefit is recommended to reduce the risk of major adverse CVEs and heart failure hospitalization.

- In patients with T2D and established ASCVD or multiple risk factors for ASCVD, the use of a glucagon-like peptide-1 receptor agonist (GLP1-RA) with demonstrated CV benefit (liraglutide > semaglutide > exenatide extended release) is recommended to reduce the risk of major CVE.
- For many patients, use of either an SGLT2i or a GLP1-RA to reduce CV risk is appropriate.

Appendix A7.11 summarizes pharmacotherapeutic glycemic control in patients with T2D.

Renoprotective and cardioprotective strategies

RASi: ARB and ACEi are the cornerstone therapeutic strategies to reduce proteinuria, reduce progressive renal functional decline, and reduce hospitalization for heart failure in DKD.

Sodium glucose cotransporter 2 inhibitors (SGLT2i):

- SGLT2i are hypoglycemic agents that, when added to maximally tolerated RASi in patients with T2D with albuminuria, further reduce albuminuria, progressive kidney function decline, and adverse CV outcomes above what can be achieved with RAASi alone.
- Protective mechanisms are thought to involve natriuresis and reduced intraglomerular filtration pressure via efferent arteriolar vasodilation mediated by tubuloglomerular feedback.
- Caution is advised for patients with recurrent urinary tract infections, genital yeast infections, and peripheral arterial disease. Because the hypoglycemic effect of SGLT2i depends on glomerular filtration, its hypoglycemic effect is attenuated with eGFR less than 45 mL/min/1.73 m^2.
- The use of SGLT2i is associated with euglycemic diabetic ketoacidosis. See **Chapter 2: Acid-Base and Potassium Disorders**.
- SGLT2i should not be started in patients receiving dialysis.

The nonsteroidal mineralocorticoid antagonist finerenone also reduces proteinuria and decline in kidney function and enhances cardioprotection above and beyond that conferred by RASi alone in patients with T2D.

GLP1-RAs are hypoglycemic agents that inhibit hunger, reduce body weight, and confer renoprotective and cardioprotective effects.

Dipeptidyl peptidase-4 (DPP-4) inhibitors may reduce proteinuria, but none are currently approved by the FDA for DKD.

BP control

- HTN occurs in approximately 40% of T1DM and 70% of T2D.
- Higher BP is associated with both development and progression of DKD.
- Progressive lowering of BP to 120 mm Hg was associated with improved renal and patient survival. However, systolic blood pressure (SBP) less than 120 mm Hg or DBP

less than 70 mm Hg is poorly tolerated and associated with increased incidence of MI and mortality. The latter is thought to reflect reduced coronary perfusion during diastole, particularly in patients with underlying coronary artery disease (Irbesartan Diabetic Nephropathy Trial).

Recommendations

- Maintain SBP less than 130 mm Hg and DBP less than 80 mm Hg.
- For DKD with albuminuria, the antihypertensive regimen should include an ACEi or ARB. The interested readers can see **Appendix A7.12** for a discussion on the use of ACEI versus ARB.
  - DM1 and T2D: Use ACEi or ARB in normotensive patients with urinary albumin-to-creatinine ratio 30 mg/g or higher who are at high risk for DKD or its progression. High risk for DKD or its progression is defined as having increasing albuminuria in the microalbuminuria range, macroalbuminuria, declining GFR, increasing BP, presence of DR, elevated lipids and/or uric acid concentrations, or family history of HTN, macrovascular disease, or DKD.
  - Combination therapy with ACEi and ARB in DKD is not advised due to unacceptable increase in adverse events (ie, impaired kidney function and hyperkalemia). In addition, the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial showed no significant benefit in primary end point (progression of kidney disease), mortality, or CVEs.
  - Aliskiren (renin inhibitor) should not be used in combination with either ACEI or ARB due to increased risk of stroke and adverse events (ie, hyperkalemia, hypotension, and ESKD or death due to kidney disease)—Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE).

Lipid management

Lowering LDL-C with statin-based therapies reduces the risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD with or without DM.

Recommendations:

- Use of LDL-C (statins or statin/ezetimibe combination) is recommended to reduce the risk of major atherosclerotic events with patients with diabetes and CKD including kidney transplant recipients. There is no evidence to suggest improvement in kidney disease outcomes with statin therapy.
- *Initiating* statin in patients with diabetes who are about to receive or already receiving dialysis is NOT recommended. Statins provide little or no benefit in death rates due to CVD events in dialysis patients with diabetes and appear to increase the risk of hemorrhagic stroke.
  - A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA) revealed no significant benefit on primary CV outcome (cardiac death or nonfatal MI and fatal or nonfatal stroke); risk of hemorrhagic stroke increased by greater than 5-fold. Two-fold increased hemorrhagic stroke risk also noted in Die Deutsche Diabetes Dialyse Studie (4D).
  - Study of Heart and Renal Protection (SHARP) trial (combined simvastatin 20 mg/ezetimibe 10 mg): no significant reduction in primary outcome of major

atherosclerotic events in over 3,000 patients on dialysis

Other considerations in the evaluation and management of DKD

Without a kidney biopsy, DKD is a diagnosis of exclusion.

A thorough history and physical examination is foundational in guiding a potential differential diagnosis, particularly in considering systemic or familial diseases.

- In patients with macroalbuminuria without retinopathy, especially if DM has been present for less than 10 years, consider evaluation for non-DKD.
- Significant hematuria should also trigger kidney biopsy consideration. Patients with diabetes with heavy proteinuria and hematuria, with or without more rapid loss of kidney function than expected for uncomplicated DKD, should be assessed serologically to rule out the presence of treatable diseases, independent of diabetes.
  - Serologies to consider in evaluating proteinuria with or without hematuria: serum and urine protein electrophoresis/immunofixation; hepatitis B/C; serologic testing for syphilis; HIV; complement C3/C4; ANA/anti-dsDNA if there is reasonable pretest probability; and PLA2R antibody (if there is nephrotic range proteinuria)
  - Serologies to consider for nonnephrotic proteinuria, hematuria, and especially with a more rapid decline in kidney function: Antinuclear cytoplasmic antibodies; complement C3/C4; LDH/haptoglobin; ANA/anti-dsDNA. Other serologies and genotyping may also be relevant depending on the clinical presentation.

Other management considerations

- Nonmedical strategies to slow down progression of DKD: smoking cessation, weight loss
- The dose of insulin is typically reduced with declining eGFR.
- Autonomic neuropathy may mimic and thereby exacerbate uremic symptoms.

SICKLE CELL DISEASE (SCD)

Genetic Inheritance and Frequency

- SCD is due to the inheritance of a missense mutation on chromosome 11 in the β-globin gene that leads to a glutamic acid to valine substitution in the hemoglobin A β subunit. SCD is inherited as an autosomal co-dominant trait and affects individuals who are homozygous for the β S allele (HbSS) as well as those with compound heterozygous variants, including sickle hemoglobin C (HbSC) disease, sickle β-thalassemia (HbSβ), and other rare genotypes, in which the β S allele is coinherited with other rare Hb variants.
- The β^0 thalassemic mutation confers a complete absence of β-globin synthesis; the β^+ mutation confers a decrease in β-globin synthesis. These mutations variably reduce the amounts of normal hemoglobin (HbA) synthesis depending on the nature of the mutation. Patients with HbSS or HbSβ^0 thalassemia typically have a more severe SCD phenotype compared to those with HbSC or HbSβ^+ thalassemia.
- In the United States, SCD is classified as a rare disease, with approximately 100,000 individuals affected. There are approximately 2,600 affected live births per year. Sickle

cell trait (SCT) affects 6% to 9% of the U.S. African American population. SCD and SCT also occur in individuals from South Asia.

Renal Manifestations

Sickle cell nephropathy (SCN) encompasses a wide range of both tubular and glomerular functional and anatomic abnormalities. Clinical manifestations are due to the generation of a sickle shape of RBCs in patients with the mutation(s), inducing vaso-occlusive thrombotic events, ischemia, and inflammation upon Hb deoxygenation in the systemic micro- and macrovascular circulations. **Table 7.15** summarizes renal manifestations of SCD.

Table 7.15 Renal abnormalities in sickle cell disease

Glomerular manifestations	• Early: Hyperfiltration, glomerular hypertrophy
	• Late:
	  • Microalbuminuria, proteinuria
	  • Glomerular lesions: FSGS (most common); others: MPGN pattern of injury, SCD glomerulopathy (glomerular hypertrophy with or without mesangial hypercellularity), TMA
	  • Progressive CKD and ESKD

Medullary manifestations	• Hematuria (microscopic or macroscopic) from medullary ischemic infarction • Concentrating defect (hyposthenuria or isosthenuria, urine osmolality <450 mOsm/kg) • Obstructive uropathy (from sloughed papillary necrosis) • Medullary carcinoma (occurs almost exclusively in sickle cell trait)

Proximal tubular manifestations	• Supranormal PT function
	  • ↑Reabsorption of Na^+, PO_4^{2-}, β2-microglobulin
	  • ↑Secretion of uric acid and creatinine (Cr-based eGFR equations may overestimate true GFR)

Distal tubular manifestations	• Incomplete RTA • Impaired concentrating ability (hyposthenuria or isosthenuria, urine osmolality <450 mOsm/kg)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MPGN, membranoproliferative glomerulonephritis; SCD, sickle cell disease; TMA, thrombotic microangiopathy.

Cortical manifestations

Early alterations:

- Hyperfiltration, glomerular hypertrophy
- Supranormal proximal tubular function:
  - Increased reabsorption of sodium, phosphate (can contribute to hyperphosphatemia), β2-microglobulin
  - Increased secretion of:
    - Uric acid (in early disease with good kidney function, serum uric acid level may be normal despite increased uric acid production)

- Creatinine (thus eGFR based on SCr may be greatly overestimated). Studies comparing cystatin c (CystC)-based *or* creatinine-based Modification of Diet in Renal Disease (MDRD) *or* CKD Epidemiology Collaboration (CKD-EPI) equations suggested that CystC-based CKD-EPI equation best estimates GFR in patients with SCD. Further studies are needed.

  FYI

  CystC levels may be increased in high cell turnover states (such as hyperthyroidism, steroid use, malignancy, advanced age, gender and ethnicity, fat mass, and diabetes). In 2023, the CystC estimating equation that excluded race had not been validated specifically yet in adult patients with SCD. In children, two studies suggested that the chronic kidney disease in children (CKiD) Schwartz formula appeared to be the best current option for estimating GFR in children.

Late alterations:

- Similar to DKD and other kidney diseases, glomerular hyperfiltration in patients with SCD can lead to microalbuminuria, proteinuria, glomerulosclerosis, and progressive CKD.
- Albuminuria is most prevalent in patients with HbSS or HbSβ^0 thalassemia compared to those with other SCD genotypes. It is associated with older age, low Hb concentrations, high levels of hemolysis markers, high levels of kidney injury molecule 1 (KIM1), and elevated echocardiography-measured tricuspid regurgitant jet velocity. Albuminuria is associated with progressive decline in kidney function.
- Glomerulopathy:
  - FSGS pattern of injury is the most common glomerular lesion in SCD and is closely associated with glomerular hypertrophy.
  - MPGN pattern of injury commonly occurs without IC deposits and may be associated with blood-borne viral infections from transfusions.
  - SCD glomerulopathy, defined as glomerular hypertrophy with or without mesangial hypercellularity, may be seen.
  - TMA may be seen and is associated with a history of retinitis.

Medullary manifestations

Impaired concentrating ability

- Leads to the production of hyposthenuric or isosthenuric urine (urine osmolality <450 mOsm/kg) even in the presence of volume depletion
- Patients may present with polyuria, nephrogenic diabetes insipidus, hypovolemia, and in young patients, nocturnal enuresis. This defect may be reversible with blood transfusion in young patients but becomes uncorrectable by age 15.

Hematuria (microscopic or macroscopic)

- 10% bilateral, left kidney affected 4 times more than right due to increased venous pressure within the longer left renal vein when compressed between the aorta and the superior mesenteric artery (a.k.a. nutcracker phenomenon).
- Pathogenesis: Low oxygen tension, low pH, and high osmolality of the renal medullary environment predispose RBCs in the vasa recta to sickle. Sickling leads to increased blood viscosity, microthrombus formation, and ischemic necrosis. The latter can cause structural changes, leading to RBC extravasation and hematuria. Severe medullary

ischemia can cause papillary necrosis and infarction that manifests clinically as painless gross hematuria.

Acute obstructive uropathy

- Sloughing of necrotic papillae into the renal pelvis can lead to obstructive uropathy.
- Sloughed necrotic papillae can give the appearance of "egg in a cup" or "golf ball and a cup" on contrast CT urography. See **Figure 6.4** in **Chapter 6: Tubular, Interstitial, and Cystic Disorders**.

Tubular manifestations

- Hyperkalemia due to impaired potassium secretion despite normal RAAS
- Hyperphosphatemia
  - Proximal tubular hyperfunctioning with increased phosphate reabsorption via sodium phosphate cotransporters in early disease
  - Reduced filtration of phosphate in advanced kidney disease
- Incomplete RTA: This is typically not clinically significant but can be unmasked with reduction in GFR.
  - Voltage-dependent hyperkalemic distal RTA: Patients fail to secrete both H^+ and K^+, thus urine pH greater than 5.5.
  - Selective aldosterone deficiency distal RTA: Patients have hyperkalemia-induced suboptimal ammoniagenesis, but can secrete H^+; thus, urine pH can be less than 5.5. These patients respond to fludrocortisone.

CKD and ESKD

- Factors associated with progression of CKD to ESKD: HTN, nephrotic range proteinuria, severe anemia, vaso-occlusive crisis, acute chest syndrome, stroke, βS-gene haplotype, pulmonary HTN, and the presence of certain genetic variants, including APOL1, HMOX1, and ACKR1
- Protective factors
  - Higher fetal hemoglobin (HbF) levels and intact α-globin genes/genotype have been suggested to be protective against SCN and vaso-occlusive complications.
  - Coinheritance of α-thalassemia appears to be protective against proteinuria and SCN.
  - Some but not all studies suggest that hydroxyurea may reduce proteinuria and/or hyperfiltration.
- Special considerations of CKD in SCD: Hb target with erythropoiesis-stimulating agent (ESA) use should not exceed 10.5 g/dL.

Management of SCD and Anemia

Management of anemia

SCA may be managed by preventive disease-modifying and supportive measures. Disease-modifying options to reduce or prevent hemolysis and anemia include the use of

hydroxyurea (hydroxycarbamide), inhibitors of HbS polymerization, or direct gene therapy.

Hydroxyurea is traditionally used to increase HbF relative to HbS levels, thereby reducing sickling of RBCs.

Voxelotor is an oral agent designed to bind HbS with a 1:1 stoichiometry and increase its affinity for oxygen, thereby inhibiting HbS polymerization and thus sickling of RBCs and hemolysis. In a clinical trial involving 274 patients with SCD, 51% of patients on voxelotor 1,500 mg daily achieved a Hb response, defined as an increase in Hb of at least 1 g/dL after 24 weeks, compared with 6% in the placebo group.

Gene therapies for SCD include Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel). Casgevy uses genome editing technologies to modify patient's own stem cells to increase HbF production. With Lyfgenia, patient's blood stem cells are genetically modified to produce HbA^{T87Q}, a gene therapy–derived Hb that functions similarly to the normal adult HbA. RBCs containing HbA^{T87Q} have a lower risk of sickling and vaso-occlusion.

Indirect supportive therapies include nutrient supplementation, blood transfusions, and possibly the use of ESAs.

Nutrient replacement

- Folate 1 mg daily for all patients unless already adequately supplemented with diet
- Consider multivitamin without iron supplements daily.
- For nontransfused iron-deficient adults, consider iron supplements, although caution must be exercised due to clinical data suggesting lower sickling risk with iron deficiency.

Blood transfusions and use of ESAs

With the use of blood transfusions or ESA, it should be noted that the goal Hb and rate of correction are recommended to be no more than 10 g/dL and less than 1% to 2% per week, respectively. Higher Hb levels and more rapid correction of anemia may precipitate vaso-occlusion.

- Blood transfusions may be considered to reduce the concentration of HbS to 30% or less in specific high-risk (eg, pregnancy, general anesthesia) or life-threatening conditions (eg, stroke, acute chest syndrome, symptomatic aplastic crisis).
- The use of ESA in SCD is undefined due to limited data. Regardless, ESA may be considered in selected individuals at the discretion of the health care provider. If ESA is used, great care must be exercised in dosing to avoid a rapid increase in RBC production and the potential risk of vaso-occlusive complications. In individuals receiving hydroxyurea, ESA dosing may need to be higher due to the inherent bone marrow suppressive effect of hydroxyurea. Of note, blood transfusions provide a higher proportion of HbA compared with stimulating endogenous RBCs with an ESA.

Management of hematuria

- Conservative: bed rest, volume repletion, rule out papillary necrosis
- For persistent hematuria, consider vasopressin or aminocaproic acid (synthetic inhibitor of the plasmin-plasminogen system) 2 to 3 g daily over several days, not to exceed 12 g daily due to the risk of thrombosis.

- For medical therapy failure or life-threatening bleeding, arterial embolization or surgical intervention must be considered.

Management of proteinuria

- In children, cohort studies suggest that chronic red cell transfusions before age 10 years might reduce hyposthenuria and albuminuria. A similar beneficial effect in adults has not been demonstrated.
- Renin-angiotensin system inhibition is effective in attenuation of microalbuminuria and macroalbuminuria, but dosing may be limited by hypotension and hyperkalemia. Sustained benefit on GFR decline has not been demonstrated. Some studies suggest that hydroxyurea may also reduce albuminuria, but not GFR decline.
- One small pilot clinical trial suggested that the oral Hb-oxygen affinity modulator voxelotor may reduce albuminuria in patients with SCD.
- Crizanlizumab is an antibody designed to inhibit P-selectin–mediated adhesion of inflammatory cells to the endothelium, thereby preventing vaso-occlusion. The effect of crizanlizumab on albuminuria and kidney function in patients with SCN is under clinical investigation.
- In a real-world observational study, L-glutamine appeared to be renoprotective in patients with SCD.

Renal Manifestations of SCT

With the exceptions of hematuria and renal medullary cancer (discussed below), renal manifestations of SCD are generally less common and less severe in patients with SCT than those with homozygous HbSS.

Renal medullary cancer

- Seen almost exclusively in patients with SCT and occurs at a relatively young age, averaging 21 years (20-30 years old). Intense exercise-induced hypoxia with increased sickling has been suggested to be contributory to the development of renal medullary carcinoma and a modifiable risk factor.
- The presence of flank or abdominal pain or continued or persistent macroscopic hematuria with or without clots should prompt further evaluation with both cystoscopy and ureteroscopy to exclude renal medullary cancer.
- Aggressive metastatic disease is usually present at diagnosis and portends a poor prognosis (median survival 3 months following diagnosis).

Others

Rhabdomyolysis, impaired urinary concentration, hematuria, papillary necrosis, and sudden death can occur in patients with SCT. Among African Americans with SCT and polycystic kidney disease, cystic hemorrhage is more common and progression to ESKD is more rapid.

Kidney Transplantation in Patients With SCD

- 1-Year graft survival exceeds 60% to 80%.
- Although survival of SCD kidney transplant recipients is inferior to matched African American transplant recipients without SCD, survival of SCD transplant recipients is comparable with that of matched patients with diabetes.
- Kidney transplant may be complicated by allograft venous thrombosis, deep vein thrombosis, and vaso-occlusive crises.
- In the current era of transplantation, desensitization protocols may allow transfusion-related highly sensitized patients to undergo a successful kidney transplant. Sickle cell transplant recipients have higher risks of infection due to autosplenectomy, avascular necrosis with chronic steroid use, and sickle cell crises due to anemia correction following a successful transplant.

VIRAL NEPHRITIDES

Human Immunodeficiency Virus (HIV)

HIV may be associated with (1) HIV-associated nephropathy (HIVAN), (2) HIV-associated immune complex kidney disease (HIVICK), (3) combined antiretroviral treatment (cART) nephropathy, and (4) TMA. With the current use of effective cART, many patients with HIV now are presenting with other CKDs such as DKD, FSGS, and hypertensive nephrosclerosis.

HIV-associated nephropathy (HIVAN)

Epidemiology

- Now rare in the era of cART
- Predominantly observed in African Americans
- Associated with severe/advanced HIV (ie, CD4 <200 cells/mm^3, high viral load)

Clinical manifestations

- Nephrotic range proteinuria, hematuria
- Normal to enlarged kidneys on ultrasound due to microcyst formation, edema

Pathogenesis

- Genetic susceptibility: APOL1
- Direct renal infection mechanistically important; antiviral treatment cures the disease.

Histopathology (**Figure 7.22**):

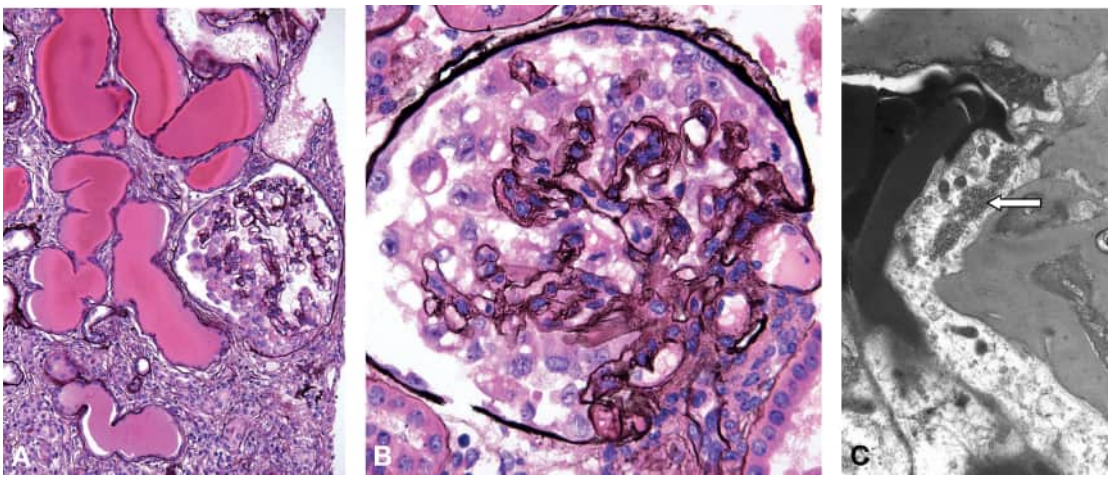


FIGURE 7.22 Human immunodeficiency virus–associated nephropathy. A. Cluster of dilated tubules with plasma protein casts and collapsing glomerulopathy (Jones silver ×100). B. Collapsing glomerulopathy showing capillary collapsing with podocyte hypertrophy, hyperplasia, and cytoplasmic vacuoles (Jones silver ×400). C. Tubuloreticular inclusion (arrow) in glomerular endothelial cell. These disappear with highly active antiretroviral therapy (×15,000).

- **LM**: collapsing FSGS, tubular microcystic dilatation with proteinaceous casts, and variable acute tubular injury, tubular atrophy, lymphocytic infiltrates, interstitial fibrosis
- **EM:** presence of tubuloreticular inclusions in endothelial cell cytoplasm in untreated patients

Natural history/prognosis: rapid progression to ESKD if untreated
Management: cART, RAASi, GC therapy only if rapid decline in kidney function despite cART AND absence of superimposed/opportunistic infections

HIV-associated immune complex kidney (HIVICK)

Background

- Typically occurs in patients with HIV duration 10 years or more
- Most common diagnosis for patients with HIV undergoing kidney biopsy
- Reported lesions: IgAN, lupus-like GN, MN, membranous/mesangial proliferative GN, PIGN, immunotactoid/fibrillary GN
- cART does not reduce the incidence of HIVICK.

NOTE

Since IgAN is rare in African Americans, the presence of IgAN should raise the possibility of concurrent HIV infection.

Clinical manifestations: NS common, hematuria, HTN, laboratory findings seen with IC GN including positive ANA, low C3

Histopathology

- IF: notable for variable Ig/complement staining, "full house" of Ig may be present.
- EM: IC deposits, endothelial cell tubuloreticular inclusions

cART nephropathy

Mitochondrial dysfunction, Fanconi syndrome, AKI/ATN

- Nucleotide analog reverse transcriptase inhibitors
- Most well recognized: tenofovir
- The use of tenofovir alafenamide (TAF) instead of tenofovir disoproxil fumarate (TDF) has reduced the incidence of tenofovir nephrotoxicity.
- Mitochondrial injury may be seen on EM as giant mitochondria with atypical shapes and broken or absent cristae (**Figure 7.23**).

Crystal-induced nephropathy/urolithiasis: protease inhibitors (eg, indinavir, atazanavir)

MPGN pattern of injury: the fusion inhibitor enfuvirtide

See **Table 10.1** in **Chapter 10: Pharmacology** for a complete list of cART effects on the kidneys.

Diabetic nephropathy

- Emerging as a common cause of kidney disease in patients with HIV undergoing kidney biopsy
- In the Veterans Aging Cohort Study, the concurrent presence of HIV and diabetes mellitus was associated with a worse prognosis than either condition alone.

Thrombotic microangiopathy

- May be seen with advanced HIV not treated with cART
- Pathogenesis thought to involve direct HIV-induced endothelial cell injury
- Affected individuals may have low ADAMTS13 levels.
- Response to GC and PLEX may be expected.

Kidney transplantation in patients with HIV

- May be considered if undetectable viral load and CD4 greater than 200 cells/mm^3

NOTE

Major drug interaction: Protease inhibitors (eg, darunavir, ritonavir) can markedly increase CNI levels. Less than 5% of usual CNI dose is typically given to achieve therapeutic level.

Also see **Chapter 9: Kidney Transplantation and Chapter 10: Pharmacology** for cART and immunosuppressive drug-drug interactions with cART.

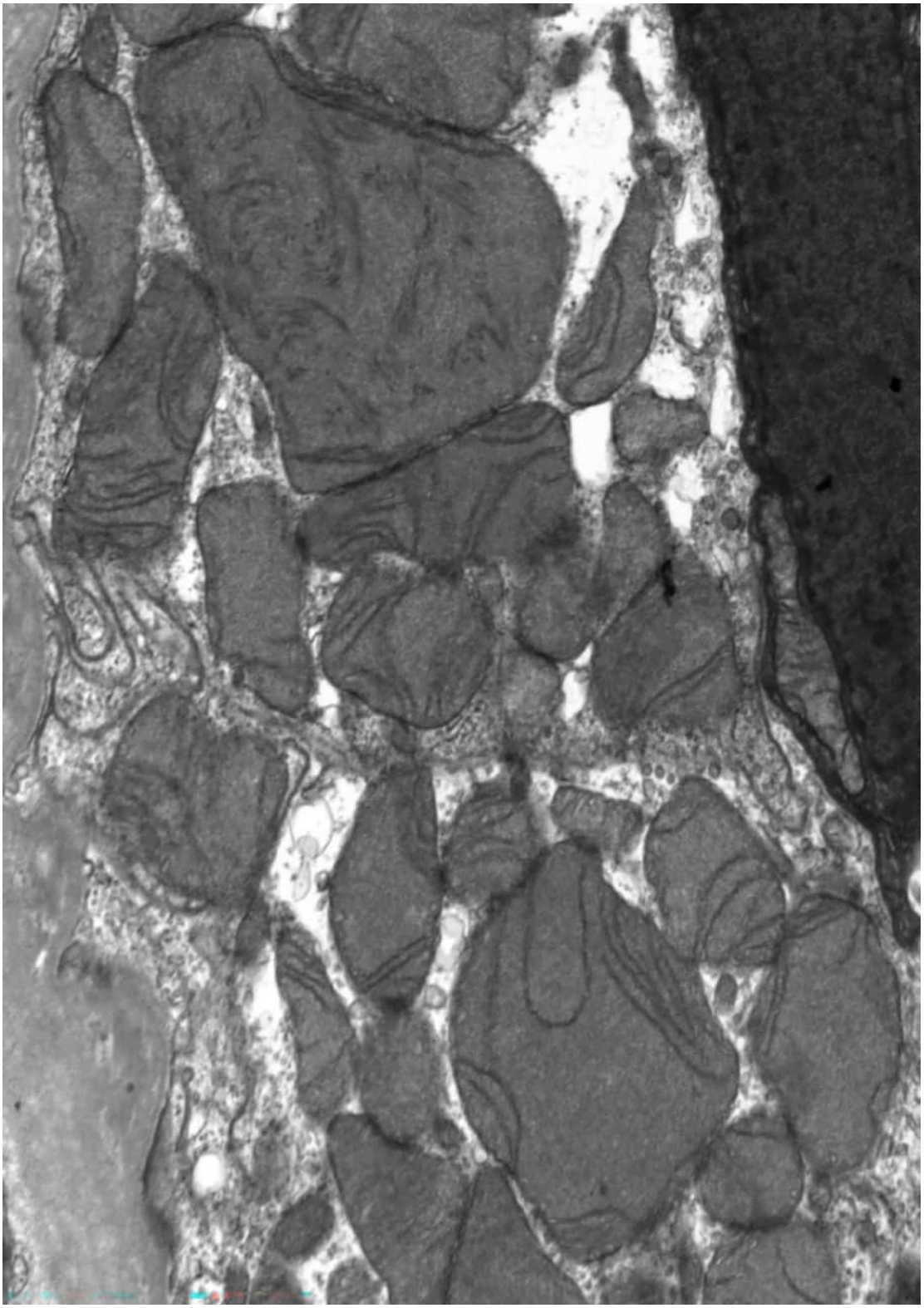


FIGURE 7.23 Tenofovir-related mitochondrial injury. Electron microscopy showing enlarged atypical proximal tubular mitochondria with broken cristae associated with nucleotide reverse transcriptase inhibitor (tenofovir) treatment (×10,000).

Hepatitis A

- Most common kidney presentation is ATN.
- Other possible lesions: tubulointerstitial disease, IC-mediated proliferative GN
- Renal recovery typically parallels liver recovery.

Hepatitis B

- Most commonly associated GN is MN without (but may be with concurrent) anti-PLA2R.
- Other notable associated lesions: MPGN pattern of injury, IgAN (in association with chronic liver disease, particularly with alcoholism), PAN (IC deposits formed by HBsAg and anti-HBs antibody [IgM] along vessel walls)

Management of hepatitis B

- Antiviral therapy: First-line agents include tenofovir and entecavir. If tenofovir is used, TAF is preferred to TDF due to the potential risk of additional renal injury. Alternatively, adefovir, lamivudine, and telbivudine may be used, but at the risk of high rate of resistance.
- Consider GC (ie, prednisone 1 mg/kg/d for 2 weeks) and PLEX prior to antiviral therapy in PAN.
- In patients with (crescentic) RPGN from HBV, consider a short course of high-dose GC with or without CYC or RTX. If RTX is used, preventive antiviral therapy must also be administered to prevent HBV reactivation.
- Nonspecific therapies: renin-angiotensin inhibition, BP control

Hepatitis C

For a detailed description of the prevention, diagnosis, evaluation, and treatment of hepatitis C, see the KDIGO 2018 Clinical Practice Guidelines.

Clinical extrahepatic manifestations of hepatitis C

Cryoglobulinemia, IC and lymphoproliferative disorder with associated arthralgias, fatigue, palpable purpura, digital ischemia, renal disease, peripheral neuropathy, vasculitis involving the CNS, hypocomplementemia

IC-MPGN with or without cryoglobulinemia is the most common glomerular pattern of injury seen with hepatitis C.

- Cryoglobulins are Igs directed against the Fc portion of anti-HCV antibody. That is, these cryoglobulins have rheumatoid factor activity.
- Laboratory findings: positive rheumatoid factor, hypocomplementemia
- Chronic active HCV infection may be associated with B-cell lymphoproliferative diseases, with the most common monoclonal gammopathy being IgM, κ LC.
- Clinical manifestations: asymptomatic hematuria and proteinuria, NS, slowly progressive CKD, or RPGN

- EM: cryoglobulins composed of curvilinear 30-nm microtubules

Other HCV-associated renal lesions: MN, fibrillary/immunotactoid GN, PAN

Clinical impact of hepatitis C

- Chronic hepatitis C correlates with the incidence of T2D and adverse outcomes.
- Successful treatment with DAA agents against HCV is associated with improvement in insulin resistance and reduced incidence of new-onset T2D.
- The incidence of ESKD, ischemic stroke, and acute coronary syndrome is reduced among successfully treated HCV patients with T2D in a large prospective cohort from Taiwan.
- Patients with T2D and insulin resistance are at increased risk for hepatocellular carcinoma.
- HCV in the dialysis patient:
  - Prevalence is 8% to 9%.
  - Seroprevalence of HCV increases with dialysis vintage.
  - HCV-infected hemodialysis patients have decreased quality of life and increased mortality compared to their noninfected counterpart.
  - HCV infection may reduce both patient and allograft survival in the kidney recipient. However, the advent of DAA should improve outcomes in hepatitis C–positive kidney transplant recipients. See **Chapter 9: Kidney Transplantation**.

Management

- Testing for hepatitis B should be done before treating for hepatitis C. Patients with both hepatitis B and C should be referred to a hepatologist.

Antiviral therapy: American Association for the Study of Liver Diseases and Infectious Diseases Society of America, HCV Guidance (online).

- Antiviral therapy is recommended for all patients with chronic HCV infection, except for those with short life expectancies.
- Patients with glomerular diseases due to hepatitis C should be treated as follows:
  - If stable kidney function and/or nonnephrotic proteinuria, treat with DAA.
  - If cryoglobulinemic flare, NS, or rapidly progressive kidney failure, treat with immunosuppressive agents (with or without PLEX) and DAA.
- In patients with histologically active HCV-associated glomerular disease who do not respond to DAA, particularly those with cryoglobulinemic kidney disease, IST should be implemented. RTX is the preferred first-line immunosuppressive treatment as long as hepatitis B is not also present.
- The specific DAA regimen chosen should be based on the HCV genotype and subtype, the viral load, prior treatment history, drug interactions, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities.
- Patients with GFR 30 mL/min/1.73 m^2 or more (CKD G1-G3b) should be treated with any licensed DAA-based regimen.

- Patients with GFR less than 30 mL/min/1.73 m^2 (CKD G4-G5D) should be treated with a DAA regimen without sofosbuvir or ribavirin.
- Kidney transplant candidates should be treated in collaboration with the transplant center to optimize the timing of therapy.

Coronavirus Disease 19 (SARS-CoV-2, COVID-19)

- Most common renal manifestation is AKI associated with sepsis.
- Collapsing FSGS is most commonly reported, almost exclusively in patients with African ancestry who carry two APOL1 risk alleles.
- A broad spectrum of de novo glomerular diseases with proteinuria and/or hematuria and exacerbation of preexisting glomerular disease has been reported (eg, MCD, AAV, IgAN).
- TMA, which may be de novo or recurrent associated with complement dysregulation
- Treatment has not been systematically studied in this population.

Parvovirus: collapsing FSGS, MPGN, diffuse proliferative GN

Hantavirus: hemorrhagic nephritis, see tubulointerstitial diseases

BK virus: see **Chapter 9: Kidney Transplantation**.

CMV: Proliferative GN has been reported but presumed to be very rare. In kidney transplants, CMV infections involving renal tubular cells and macrophages may result in intracytoplasmic inclusions with "owl-like" appearance.

FABRY DISEASE

Background

- Second most prevalent lysosomal storage disease after Gaucher disease
- May be seen in all ethnicities and races
- X-linked inborn error of metabolism with deficiency or defect of lysosomal hydrolase α-galactosidase A (α-Gal A), an enzyme that catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3), thus leading to lysosomal accumulation of Gb3 in various cells including vascular endothelium and smooth muscle cells, cardiac muscle cells and conduction fibers, kidneys, and nerve root ganglia.

Clinical Manifestations

Neurologic: neuropathic pain in extremities, stroke at an early age

Dermatologic: telangiectasias, angiokeratomas in groin, hip, periumbilical areas, corneal opacities, thickened lips, bullous nose, hypohidrosis and associated heat/exercise or cold

intolerance, respectively

Cardiac: arrhythmias, left ventricular hypertrophy, heart failure, and valvular abnormalities

GI: abdominal pain, nausea, vomiting, diarrhea, or constipation. Often initially misdiagnosed as irritable bowel syndrome

Renal: proteinuria (both tubular and glomerular proteinuria possible), progressive CKD, Fanconi syndrome due to proximal tubular injury, polydipsia and polyuria due to distal tubular injury and associated defective urinary concentrating ability, multiple renal sinus and peripelvic cysts on imaging studies

Histopathology (Figure 7.24)

LM:

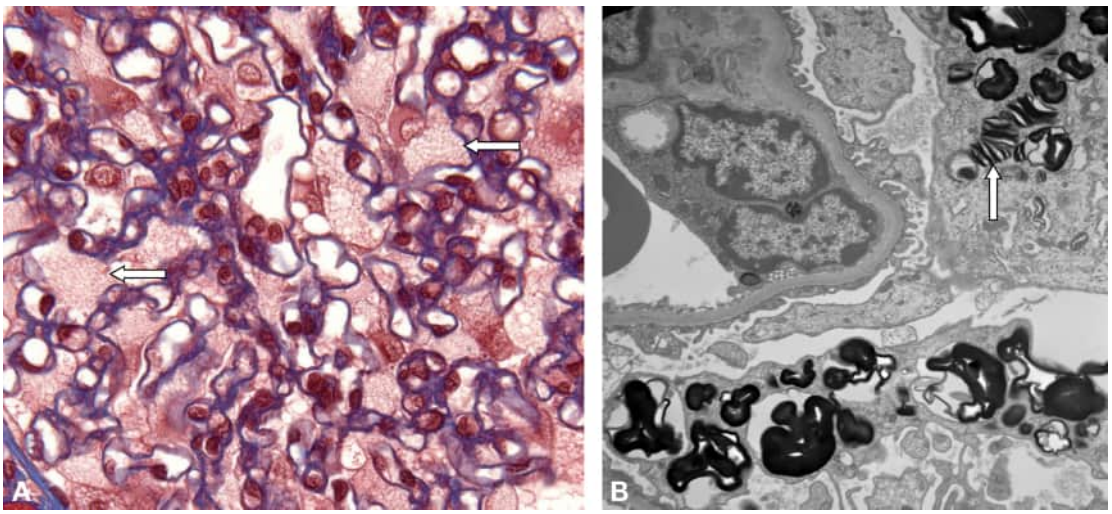


FIGURE 7.24 **Fabry disease.** A. Enlarged foamy podocytes (arrows) throughout the glomerulus (Masson trichrome ×600). B. Podocytes contain whorled and clumped electron-dense inclusions (myelin figures) composed of accumulated globotriaosylceramide. These inclusions may have a striped or "zebra body" appearance (arrow) (×10,000).

- Vacuolization/foamy appearance of podocytes, occasionally endothelial cells and rarely distal tubular epithelial cells due to glycolipid accumulation
- Nonspecific findings: FSGS or global glomerulosclerosis, tubulointerstitial fibrosis

EM: podocytes with "myeloid" or "zebra" bodies (concentric lamellated inclusions often with a striped [zebra] appearance formed by Gb3 deposits within enlarged secondary lysosomes)

NOTE

Of note, lamellar inclusions may be seen in podocytes associated with chloroquine or HC administration. Less often, these may be associated with gentamicin toxicity, silicosis, other select medications, and rarely with LMX1B mutations, Niemann-Pick disease, or Hurler syndrome.

Diagnosis

Males

- Low α-Gal A activity in leukocytes of plasma in males
- Genetic analysis may also be required in males with marginally low α-Gal A activity levels.

Females

- Female carriers may have normal to low levels of α-Gal A.
- Genetic analysis for the α-Gal A gene is required for diagnosis.

Tissue biopsy (skin or kidney) reveals characteristic findings but is typically not necessary.

Management

Enzyme (α-Gal A) replacement therapy

- Recommended for all males and females with classic presentations
- May be considered in asymptomatic female carriers or males with atypical presentations
- Enzyme replacement therapy (ERT) effectively reduces tissue deposition of Gb3 in most tissues, except for podocytes and vascular smooth muscle. Nonetheless, replacement therapy may slow kidney function decline in early disease.
- Replacement options: agalsidase alfa 0.2 mg/kg or agalsidase β 1.0 mg/kg infusion every 2 weeks. Only the β form is available in the United States. A biosimilar of agalsidase β is available in Japan (JR-051). Notable side effects: infusion reactions, development of antibodies against the enzyme.

Chaperone treatment: Migalastat is an oral medication that binds and stabilizes specific mutant forms of α-Gal. It facilitates its movement into lysosomes and increases enzyme activity. It may be used as first-line therapy in patients with amenable mutations and eGFR greater than 30 mL/min/1.73 m^2.

Gene editing: Clinical trials are in progress.

Supportive antiproteinuric care: RAASi are advised; the roles of SGLT2i, finerenone, and sacubitril/valsartan are under study.

Genetic counseling

Kidney transplantation improves survival compared to nontransplant.

SCLERODERMA AND THE KIDNEYS

See discussion of scleroderma renal crisis in **Chapter 5: Hypertension**.

CHAPTER 8

Transplant Immunobiology

Michelle J. Hickey, Phuong-Chi T. Pham, and Phuong-Thu T. Pham

BACKGROUND

- ABO blood group is the most important tissue barrier to successful kidney transplantation, followed by major histocompatibility complex (MHC) antigens.
- Non-MHC molecules, referred to as minor histocompatibility antigens or non-human leukocyte antigens (non-HLAs), can also mediate rejection (discuss below and summarize in **Table 8.1**).

Table 8.1 Transplantation antigens and their role in kidney allograft rejection

Transplantation antigens (listed in order of importance in allograft rejection)	Comments
ABO blood group	• ABO blood group antigens are strong transplantation antigen. • ABO-incompatible transplantation results in hyperacute rejection and graft loss.
Major histocompatibility antigens (MHCs) (also known as human leukocyte antigens [HLA])	• HLAs are classified into class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DQA, HLA-DP, HLA-DPA). • Fewer HLA mismatches between donor and recipient correlate better with graft survival. • 1-y graft survival is more related to HLA class II mismatching than to class I mismatching.

Transplantation antigens (listed in order of importance in allograft rejection)	Comments
	• Repeat HLA mismatch in the setting of a reallograft transplantation may trigger reactivation of memory cells and production of donor-specific antibodies.
Minor histocompatibility antigens	• MHC-related chain A (MICA) and MHC-related chain B (MICB) are examples of minor antigens expressed on endothelial cells. • Unlike the classical HLA classes I and II, they do not bind peptides and do not engage T-cell receptor. Antibodies against MICA have been shown to be associated with antibody-mediated rejection.
Non-HLAs	• Examples of non-HLAs: MICA and MICB (discussed above), AT1R, anti-endothelin-1 type A receptor (ETAR), vimentin, cardiac myosin, collagen V, and agrin • Antibodies to non-HLAs have been shown to be associated with graft rejection. • Currently, clinical tests are available to test for antibodies to MICA, AT1R, and reactivity to antigens expressed on donor endothelial cells.

ABO Blood Group Antigens

- ABO blood group antigens are expressed on the surface of red blood cells as well as in the kidneys, gastrointestinal, respiratory, and other organ systems.
- ABO-incompatible kidney transplantation results in hyperacute rejection and graft loss.
- A number of variant A antigens are known, with the A1 antigen providing more potent antigenicity than the antigen A2. Successful transplantation can be performed using A2 kidneys into O recipients and A2 and A2B kidneys into B recipients.

- Various desensitization protocols have allowed successful ABO-incompatible kidney transplantation. Discussion is beyond the scope of this chapter.

MHC, HLA Molecules

General overview

- The major histocompatibility (*MHC*) genes are located on the short arm of chromosome 6 and represent the most polymorphic genes in the human genome.
- HLAs are glycoproteins encoded by the *MHC* genes (**Figure 8.1**). The MHC molecule was first discovered in human leukocytes and is, therefore, called the human leukocyte antigen (HLA).

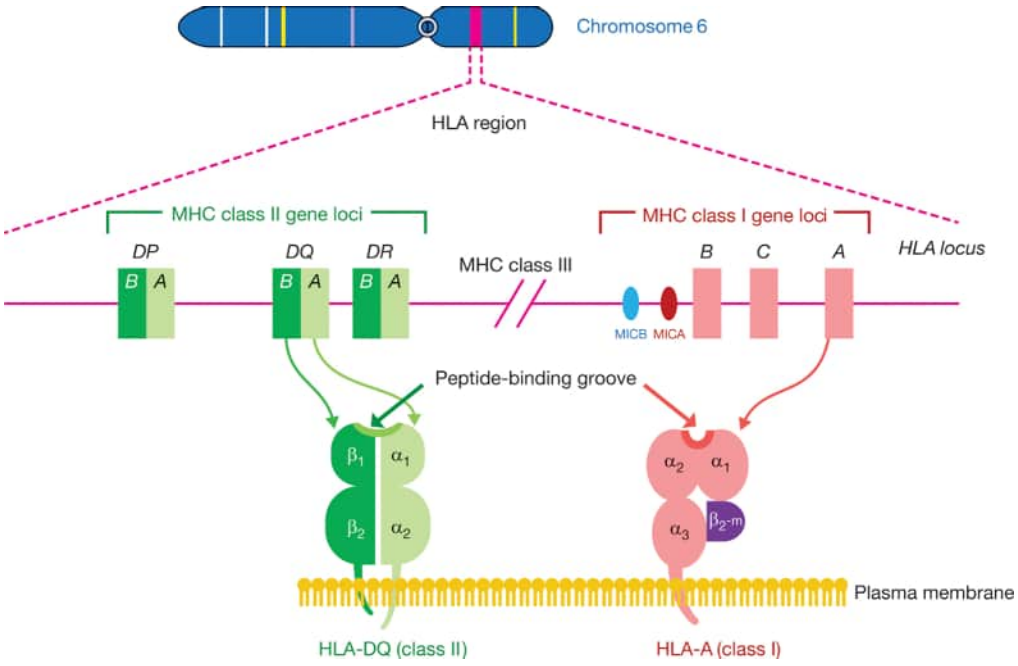


FIGURE 8.1 Major histocompatibility complex (MHC), human leukocyte antigen (HLA) molecules. Class I HLA antigens (HLA-A, HLA-B, and HLA-C) are composed of a polymorphic α or heavy chain (encoded by *HLA-A*, *HLA-B*, and *HLA-C* genes) that is noncovalently bound to a nonpolymorphic light-chain, β_2-microglobulin (β_2-m). Class II HLA antigens (HLA-DP, HLA-DQ, and HLA-DR) are composed of two noncovalently bound glycoproteins: an α chain (encoded by *DPA1*, *DQA1*, or *DRA1/3/4/5*) and a β chain (encoded by *DPB1*, *DQB1*, or *DRB1*, *DRB3/4/5*). NOTE: All HLA-DR types have the *DRB1* gene, and some contain an additional functional gene, *DRB3, DRB4, or DRB5*. The majority of polymorphisms that stimulate

alloactivation of the recipient's immune system are located in the α_1 and α_2 domains of HLA class I and in the α_1 and β_1 domains of HLA class II.

- The primary role of class I and II HLAs is to present foreign antigen to the immune system.
- In kidney transplantation, HLAs are the predominant antigens that form the targets for the immune response.
- Over 25,000 distinct HLA alleles have been defined through DNA sequencing. Despite significant diversity at the level of DNA, most polymorphisms that stimulate alloreactivity of the recipient's immune system are located in the α1 and α2 domains of the α chain of HLA class I and in the α1 and β1 domains of the α and β chains of HLA class II, respectively (discussed below).

HLA class I (see Figure 8.1)

- The classical HLA class I antigens (HLA-A, HLA-B, HLA-C) are heterodimers composed of a polymorphic, membrane-spanning α or heavy chain of 44 kDa with three external domains (α_1, α_2, and α_3), noncovalently bound and stabilized by a nonpolymorphic light chain, β_2-microglobulin (β_2-m) of 12 kDa. β_2-m is encoded by a non-MHC gene located on chromosome 15.
- HLA class I antigens are encoded by the *HLA-A, HLA-B,* and *HLA-C* genes.
- They are expressed on all nucleated cells and platelets, but not on red blood cells.
- Class I molecules generally present peptides derived from intracellular proteins (eg, viral proteins) to cytotoxic $CD8^+$ T cells (**Figure 8.2**).

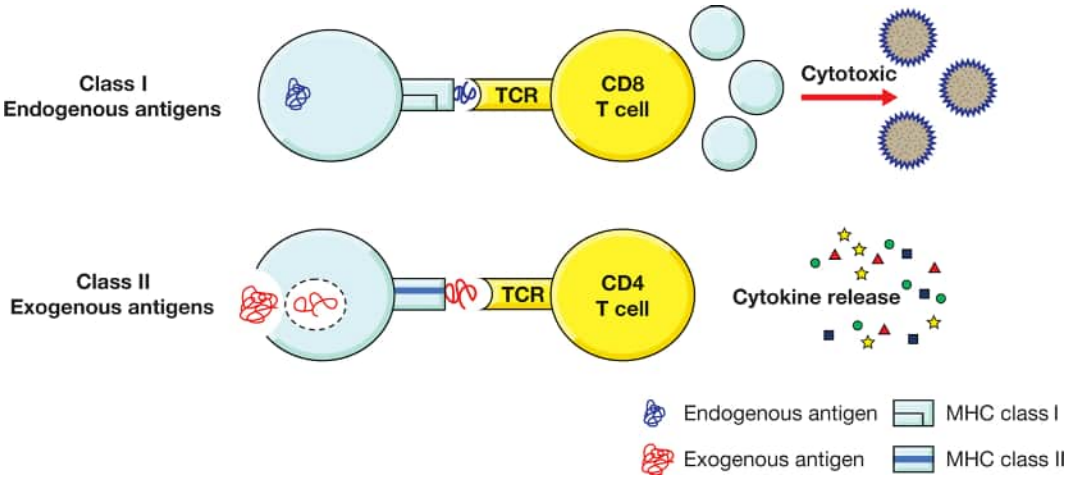


FIGURE 8.2 Antigen presentation. The endogenous pathway: Endogenous antigens are digested into peptides and loaded into class I major histocompatibility complex (MHC). The MHC-peptide complex is assembled within the cell's endoplasmic reticulum, transported through the Golgi apparatus, and expressed on the cell surface where it is recognized by $CD8^+$ T-cell receptor (TCR), leading to T-cell activation. Exogenous pathway: Exogenous antigens are degraded within endosomes and loaded into class II MHC. The MHC-peptide complex is ultimately expressed on the cell surface where it is recognized by $CD4^+$ TCR, leading to T-cell activation.

HLA class II (see Figure 8.1)

- The classical class II antigens (HLA-DP, HLA-DQ, and HLA-DR) are composed of two membrane-spanning, noncovalently bound glycoproteins: an α chain of 35 kDa (encoded by *DPA1, DQA1,* or *DRA1*) and a β chain of 31 kDa (encoded by *DPB1, DQB1*, or *DRB1*).
- Most polymorphic sites on class II antigens that stimulate alloactivation of the recipient's immune system are located in the α_1 and β_1 domains of HLA class II.
- HLA class II antigens are constitutively expressed on professional antigen-presenting cells (APCs), including dendritic cells, macrophages, and B lymphocytes. Their expression may be upregulated on activated T cells and epithelial and vascular cells (eg, renal tubular cells, glomerular endothelium, and capillaries) after exposure to pro-inflammatory cytokines.

- Class II molecules present larger peptides derived from extracellular proteins (eg, bacterial proteins) to $CD4^+$ T cells (see **Figure 8.2**).

Kidney donors and recipients in the United States are typed for HLA-A, HLA-B, HLA-Bw4/6, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1, HLA-DQA1, HLA-DP, and HLA-DPA1. For interested readers, see **Appendix A8.1** for molecular typing of HLA-Bw4 and HLA-Bw6 antigens and HLA-DRB3/4/5.

Related and Unrelated Donor/Recipient Pair: Haplotype Match Versus HLA Antigen Match

Kidney from a parent or sibling

- Each parental chromosome 6 provides a linked set of *MHC* genes (called a haplotype) to the offspring in a Mendelian codominance inheritance. Statistically, there is a 25% chance that siblings share the same two haplotypes (two-haplotype match), a 50% chance they share one same haplotype (one-haplotype match), and a 25% chance they do not share any of their parental haplotypes (zero-haplotype match or two-haplotype mismatch).
- By definition, a child is a haplotype match to each parent unless recombination has occurred (**Figure 8.3**).

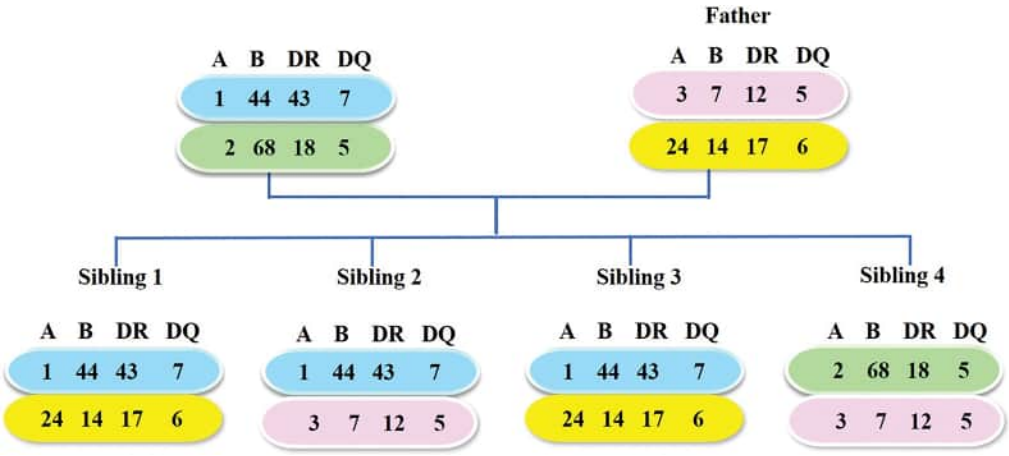


FIGURE 8.3 Inheritance of haplotypes and human leukocyte antigen (HLA) profile in four theoretical siblings when considering HLA-A, HLA-B, HLA-DR, and HLA-DQ. Sibling 1 is a one-haplotype

match to sibling 2, a two-haplotype match to sibling 3, and a zero-haplotype match to sibling 4 (or a two-haplotype *mismatch* to sibling 4).

- A kidney from a parent donor (father or mother) to a recipient offspring will have one-haplotype match.
- A kidney from a sibling donor to sibling recipient: will either be a zero-haplotype match, one-haplotype match, or two-haplotype match (see **Figure 8.3**).
- Since *HLA* genes are inherited as a set, a two-haplotype match between two siblings would indicate that the pair is not only matched at the HLA-A, HLA-B, and HLA-DR loci but is also matched at the HLA-C, HLA-DP, and HLA-DQ loci. However, if the donor and recipient are unrelated, such conclusions cannot be drawn (see haplotype match vs antigen match later).

Kidney from a related versus unrelated donor (haplotype match vs antigen match)

Consider the HLA *phenotype* of the following recipient/donor pair:

- Recipient: **A** 1, 2; **B** 8, 51; **DR** 17, 11; DQ 2, 7
- Donor: **A** 1, 3; **B** 8, 7; **DR** 17, 15; DQ 2, 6

The donor is a four out of eight HLA antigen match with the recipient (matched at 1 A, 1 B, 1 DR, and 1 DQ antigen).

- If the recipient and donor are siblings, or parent/offspring, it is possible to identify the shared haplotype as **A**1, **B**8, **DR**17, and **DQ**2, and this is a one-haplotype match.
- However, if the recipient and donor are unrelated, the HLA phenotypes of these two individuals would be called a four-antigen match because it is not known which antigens are linked on each chromosome.

United Network for Organ Sharing (UNOS) Allocation System

- In the UNOS allocation system, points are given to patients with HLA-DR match: 2 points if there are no HLA-DR mismatches with

the donor and 1 point if there is one HLA-DR mismatch with the donor. Allocation of "zero-antigen mismatch" donor kidneys is based on HLA-A, HLA-B, and HLA-DR matching between patient and donor. Therefore, a zero-mismatch refers to HLA matching at the A, B, and DR loci but does not rule out mismatching at other loci (ie, HLA-C, HLA-DP, or HLA-DQ). Consider the HLA typing of the following recipient/donor pair:

- Recipient: **A** 2, 29; **B** 7, 44; **C** 7, 16; **DR** 15, 7; **DQ** 6, 2; **DP** 23, 28
- Donor: **A** 2, 29; **B** 7, 44; **C** 8, 16; **DR** 15, 7; **DQ** 5, 2; **DP** 23, 18

The donor is a zero HLA-A, HLA-B, and HLA-DR mismatch, but is mismatched with the recipient for three HLA antigens (1 C, 1 DQ, and 1 DP). Therefore, the donor is also considered a 3 out of 12 HLA mismatch with the recipient.

- The degree of HLA mismatch between donor and recipient plays an important role in rejection risk and graft loss. In the setting of kidney transplant, fewer HLA mismatches correlate with improved graft survival.
  - One-year graft survival is more related to HLA class II mismatching than to class I mismatching.
  - Repeat HLA antigen mismatch in the setting of reallograft transplantation (second or third transplant) may trigger reactivation of memory cells and production of donor-specific antibody (DSA). DSAs are antibodies that are specific for donor antigens and can be formed prior to transplant due to pregnancy, blood transfusion, or prior transplant (referred to as preformed) or developed post-transplant (referred to as de novo). Further discussion on identification of anti-HLA antibodies is presented in a later section.

HLA-TYPING TECHNIQUES

Serotyping

HLA serotyping by serologic methods was previously performed using the complement-dependent microlymphocytotoxicity test.

Procedure

- The test is performed in a microtiter plate with multiple small wells.
- Each well is loaded with a selected antiserum, and lymphocytes from the individual to be typed are added. The antiserum is well characterized and contains strong HLA antibodies with known antigen specificity.
- After an incubation period, complement is added.

Interpretation

- If anti-HLA antibody from the antiserum binds to its specific HLA target antigen on the cell surface, the complement cascade is activated, leading to cytotoxic injury. A vital dye is added to permit visualization of the proportion of dead cells in each well when the tray is examined under phase-contrast microscopy.
- The HLA-typing antiserum does not recognize all antigens and is considered low resolution.

DNA Typing

- Molecular DNA typing is a more accurate with higher resolution HLA-typing technique compared with serotyping.
- Generally, DNA isolated from blood anticoagulated with acid citrate dextrose (ACD) is preferred for DNA-based HLA-typing methods; however, any source of cells can serve as a sample for molecular-based HLA typing, including samples isolated from biopsy.
- DNA-based HLA typing uses standardized probes, primers, or sequencing to determine an individual's HLA type.
- DNA probes hybridize to the complementary DNA nucleotide sequence that is unique to an HLA locus, allele, or groups of

alleles. DNA hybridization probe techniques allow varying levels of "antigen-level" resolution based on the method used (low to intermediate resolution), whereas sequencing provides high-resolution "allele-level" HLA typing.

- Molecular-based HLA typing reveals a much greater degree of polymorphism of the individual HLA than that detected by serologic tests.
- The HLA class I and II genes are the most polymorphic genes in the human genome. Polymorphisms are nucleic acid differences between people that result in significant genetic variation in antigens, allowing HLAs to vary slightly from person to person.

HLA Nomenclature

- The level of resolution provided by various molecular HLA-typing methods leads to complex HLA nomenclature.
- Methods that produce low-resolution typing results distinguish an antigen such as "A2," whereas high-resolution probes make it possible to distinguish alleles of that antigen, such as "A*02:01:01:02" (**Figure 8.4**).
- Intermediate-resolution HLA-typing results may include a "string" of alleles that cannot be ruled out by the method such as A*02:01/03/09/212 (for explanation, see **Figure 8.4**).

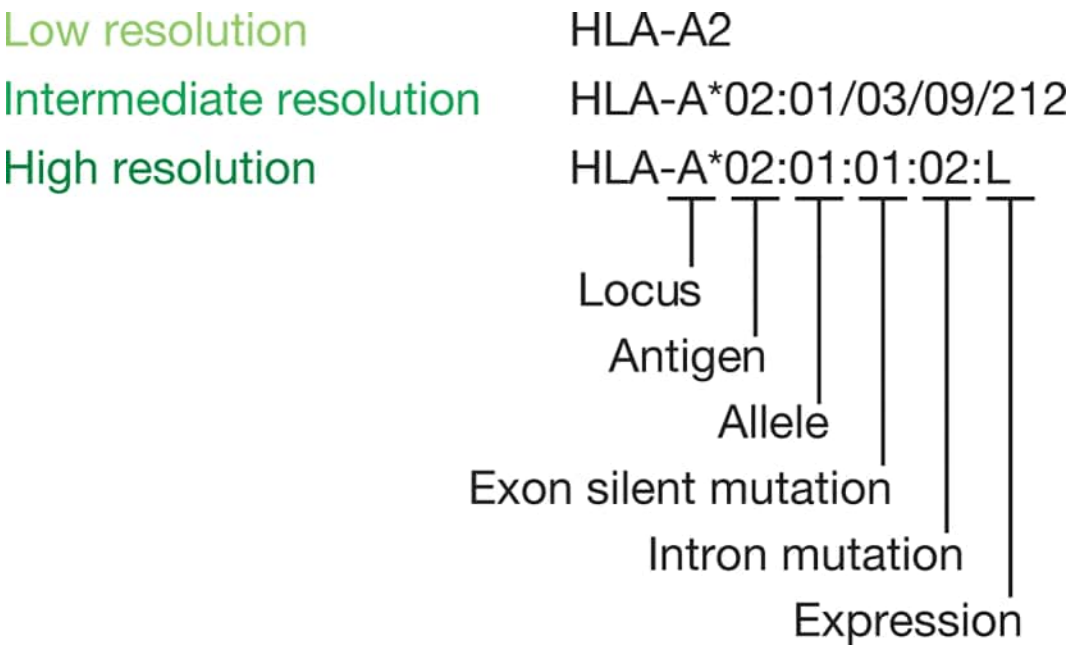


FIGURE 8.4 Human leukocyte antigen (HLA) nomenclature. Low-resolution HLA typing, performed by serology during the early days of tissue typing, defines the HLA locus (eg, A, B, C, DR) and antigen, shown here as "2." HLA typing performed by state-of-the-art molecular methods is denoted by "*." Intermediate-resolution HLA typing defines the locus, antigen, and a string of alleles that cannot be ruled out by the method ":01/03/09/212," whereas high-resolution methods define the allele as well as nucleotide substitutions in exons resulting in silent mutations and intronic mutations. Some typing results include a letter, such as "L" indicating that the antigen is known to be of "low" expression. Intermediate-resolution HLA typing is generally sufficient for solid organ transplant patients and donors, whereas high-resolution typing is required for bone marrow and peripheral blood stem cell transplant.

MINOR HISTOCOMPATIBILITY ANTIGENS

- Minor histocompatibility antigens are small endogenous peptides that occupy the antigen-binding site of the donor MHC molecules. They are encoded by genes located on different chromosomes.
- Minor histocompatibility antigens are usually recognized by $CD8^+$ cytotoxic T cells in the context of self-MHC (indirect allorecognition), leading to graft rejection.
- The nonclassical MHC class I–related chain A (MICA) and MHC class I–related chain B (MICB) are examples of minor antigen expressed on endothelial cells. The *MICA* and *MICB* genes are located on chromosome 6, close to HLA-B (**Figure 8.1**). However,

unlike the classic HLA class I, they do not bind peptides and do not engage with the T-cell receptor. Antibodies against MICA have been shown to be associated with antibody-mediated rejection (AMR).

- While transplant from an identical twin may be accomplished in the context of no immunosuppression, two-haplotype–matched siblings (fraternal twins or nontwin siblings) require immunosuppression (albeit at reduced dose) to prevent rejection due to differences in minor histocompatibility antigens.

NON-HUMAN LEUKOCYTE ANTIGENS

- Non-HLAs are antigens expressed on the allograft endothelium and are distinct from HLA.
- Non-HLAs can be classified as:
  - Alloantigens such as MICA and MICB (discussed earlier)
  - Tissue-specific autoantigens such as the angiotensin II type 1 receptor (AT1R), anti-endothelin-1 type A receptor (ETAR), vimentin, cardiac myosin, collagen V, and agrin
- Antibodies to non-HLAs are associated with poor graft outcomes. Currently, clinical tests are available to test for antibodies to MICA, AT1R, and reactivity to antigens expressed on donor endothelial cells. For example, the endothelial cell crossmatch identifies non-HLA immunoglobulin G (IgG) antibodies reactive to antigens expressed on endothelial cells. Identification of antibodies to non-HLAs that may be associated with graft rejection is an area of intense research because graft rejection and graft loss can occur in the absence of detectable HLA DSAs. Identification of non-HLA antibodies by Luminex-based methods are commercially available and were developed with the goal of providing higher throughput, sensitivity, and specificity in comparison to the currently available methods described above. These tests are currently used primarily for research and are pending additional validation.

ALLORECOGNITION PATHWAYS: DIRECT, INDIRECT, AND SEMIDIRECT ALLORECOGNITION

Direct pathway: In the direct pathway, recipient T cells recognize intact allogeneic HLAs expressed by donor cells (**Figure 8.5**).

Indirect pathway: In the indirect pathway, recipient T cells recognize peptides derived from donor HLAs presented by recipient APCs (see **Figure 8.5**).

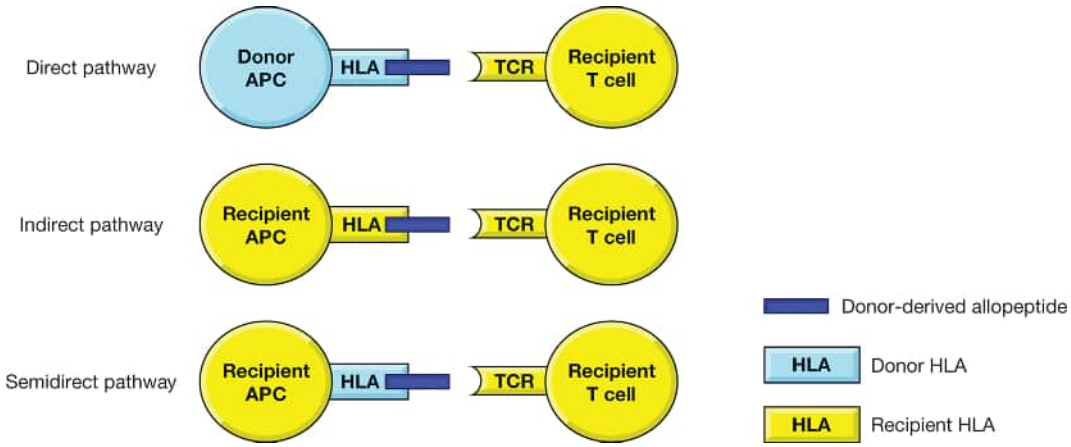


FIGURE 8.5 Direct, indirect, and semidirect allorecognition pathways. In the direct allorecognition pathway, recipient's T cells recognize intact allogeneic human leukocyte antigen (HLA) antigens expressed by donor cells. In the indirect pathway, the recipient's T cells recognize peptides derived from donor HLAs that are presented by recipient antigen-presenting cells (APCs). In the semidirect pathway, intact donor HLA is transferred to recipient APC and presents donor antigen to recipient T cells.
Abbreviation: TCR, T-cell receptor.

Semidirect way: In the semidirect way, intact donor HLAs are presented on the recipient APCs (through either membrane exchange or exosome uptake) to the recipient T cells (see **Figure 8.5**).

- Acute rejection of an allograft is primarily dependent on direct allorecognition, whereas the indirect pathway may play a greater role in chronic rejection thought to be due to the continuous shedding of donor MHC-allopeptide complexes from the graft. Such complexes are processed by recipient APCs and presented as allopeptide to recipient T cells.

- The semidirect pathway also plays an important role in chronic allograft rejection. However, the relative contribution of the direct, indirect, and semidirect allorecognition pathways to the alloresponse in the early and late post-transplantation period remains to be elucidated.

HLA ALLOSENSITIZATION

More than 30% of patients awaiting a kidney transplant in the United States are sensitized and, therefore, produce alloantibody, to HLAs.

- Anti-HLA antibodies are formed after exposure to allogeneic HLAs through pregnancy, blood transfusion, or prior transplantation.
- HLA sensitization can also develop following immune activation in patients with implantable ventricular assist devices, infections, or following surgical procedures.

Alloantibody Specificities

The specificities of HLA antibodies that an individual produces upon exposure to allogeneic HLA molecules are influenced by the individual's immunologic history as well as the individual's HLA type.

Definitions

An epitope is an approximate 15 Å region of amino acids on an antigen that is recognized by an antibody characterizing specificity and affinity.

Antibodies to "private" specificities recognize an epitope that is unique to one particular HLA molecule.

Antibodies to "public" specificities recognize an epitope that is shared by more than one HLA molecule. A common example are antibodies to the public epitope Bw4 or Bw6 that is shared by 40% or 60% of HLA-B antigens, respectively.

CREGS: HLAs that share epitopes can be grouped into the major cross-reactive groups also known as CREGs (eg, a patient's serum

containing HLA-A2 antibodies may react with HLA-A2 as well as HLA-A68, HLA-A69, HLA-B57, and HLA-B58 because these antigens share amino acid sequence motifs with HLA-A2).

Antibodies to HLA-DP are generally formed to well-characterized epitopes known as hypervariable regions primarily spanning amino acids 55 to 57 and 84 to 87 on the DP antigen. Therefore, antibodies to DP antigens are generally identified in epitope-sharing groups. For example, DP3 is also found with antibodies to DP6, DP14, and DP17 because of the shared epitopes DED (aa 55-57) and DEAV (aa 84-87); DP2 antibody is generally found with antibody to DP402 and DP105 due to the shared epitope DEE and GGPM.

An eplet is a single, or small patch, or amino acids on an antigen, approximately 3 Å in size. This is proposed to be the smallest functional region of polymorphic residues that may drive antibody specificity to HLA. The eplet-mismatch model proposes that an increased number of mismatched eplets between a patient and donor, particularly to HLA class II DR and DQ, may be associated with increased development of de novo DSA post-transplant. Comparison of the number of eplet-mismatches, an emerging area of transplant clinical research, with whole HLA mismatch (eg, a 2 DR DQ mismatch) may be useful in stratifying patients into low-, intermediate-, or high-risk groups post-transplant.

TECHNIQUES FOR DETECTION OF ANTI-HLA ANTIBODIES: GENERAL CONCEPT

- Preformed HLA antibodies of the IgG isotype may prohibit successful organ transplantation.
- The tests used to identify anti-HLA antibodies are based on assessment of reactions of anti-HLA IgG antibodies present in the patient's serum with well-characterized panels of donor lymphocytes (cell-based screening for complement-dependent cytotoxicity [CDC]) or HLAs coupled to microspheres (solid-phase screening for phenotype or single-antigen Luminex bead-based assays).

Cell-based assays

- Cell-based assays can detect strong HLA antibodies but do not always allow identification of specific antigens to which the patient has antibodies, especially in cases of broad sensitization.
- Patient's serum can be treated with dithiothreitol (DTT) to remove the effects of IgM.
- IgM antibody is often detected in sera of patients with autoimmune disorders such as systemic lupus erythematosus.

Solid-phase, bead-based Luminex technology

- Solid-phase, bead-based Luminex technology revolutionized the field of HLA antibody identification, allowing for superior sensitivity and specificity that is not possible with cell-based assays.
- Luminex-based antibody detection is used to identify HLA antibodies pretransplant to guide donor selection and risk assessment at the time of transplant and in post-transplant immune monitoring to identify DSA and correlate to biopsy findings when rejection is suspected.
- HLA antibody detection by Luminex-based methods can be performed using two different types of Luminex-bead sets, screening/phenotype beads or single-antigen beads, described below.
- Modifications of the single-antigen bead test include testing with serum dilution or using the single-antigen C1q assay that detects the ability of HLA antibodies to bind C1q (the first component of the classic complement cascade) after incubation with Luminex beads. For interested readers, see **Appendix A8.2**.

DETERMINATION OF HLA SENSITIZATION

The panel of reactive antibody (PRA) is a tool used to assess a patient's degree of sensitization to HLAs. Historically, PRA was determined by the cell-based cytotoxicity assays. A limitation of the

assay is the inability to determine antibody specificities in broadly sensitized patients. Currently, UNOS requires the use of solid-phase Luminex based to determine the presence of HLA antibodies. From the results of these tests, the calculated panel reactive antibody (cPRA) can be calculated to assess a patient's level of sensitization. The concept and utility of PRA, cPRA, and unacceptable HLAs are discussed below.

Cell-Based CDC PRA

The cross section of donors that a patient displays strong HLA DSA to, and therefore would be avoided, can be understood by incubating the patient's serum with a panel of lymphocytes that display HLAs representative of the local donor population in the cell-based CDC PRA test. This test has largely been replaced by the solid-phase Luminex cPRA.

Procedure

- In the cell-based cytotoxic PRA, the patient's serum is incubated with a panel of HLA-typed T or B lymphocytes that represent the local donor pool.
- HLA antibody in the serum binds the cell, and unbound HLA antibody is removed.
- Complement and a vital dye are then added. One molecule of complement binds to two bound HLA antibodies, and the complement cascade is initiated, resulting in perforation of the cell membrane by the membrane-attack complex (MAC) and cell lysis.
- Qualitative/semiquantitative results are read microscopically. Prolonging the complement incubation time increases the sensitivity of the test and enhances the detection of low-titer antibodies.

Interpretation

- In a positive result, the cells take up the vital dye, indicating the presence of *strong, complement-binding HLA DSA* and initiation of the complement cascade resulting in cell death.
- The percentage of positive cells over the panel, referred to as percentage panel reactive antibody (%PRA), is calculated by dividing the number of positive wells (indicated by dead cells) by the total number of wells on the panel.
- Separate panels of T and B lymphocytes identify antibodies to HLA class I or II.
- The % PRA estimates the percentage of organ donors who would be crossmatch incompatible with a transplant candidate in a given (generally geographically local) donor pool. A PRA of 80% on the HLA class I panel of cells indicates that the patient has a 20% of chance to receive a negative CDC crossmatch with a donor.

Solid-Phase Luminex PRA

Solid-phase assays employing Luminex technology use HLA-coated beads to detect and identify preformed HLA antibodies before transplantation as well as to monitor for de novo development of anti-HLA antibodies after transplantation.

Procedure

Generally, two platforms are used to identify HLA antibodies.

Screening or phenotype beads are engineered to display HLA class I or II antigens in their *native conformation.* These are produced by affixing the cell membrane harvested from a transformed cell line onto a microsphere. Each screening bead displays two haplotypes of HLAs. A "panel" of beads is constructed from an array of cells bearing various HLA phenotypes representative of the donor pool (**Figure 8.6A**).

Single-antigen beads differ in that each microsphere is affixed to only one single HLA molecule (**Figure 8.6B**). Instead of harvesting from cell lines, the HLA molecules are *recombinantly generated*.

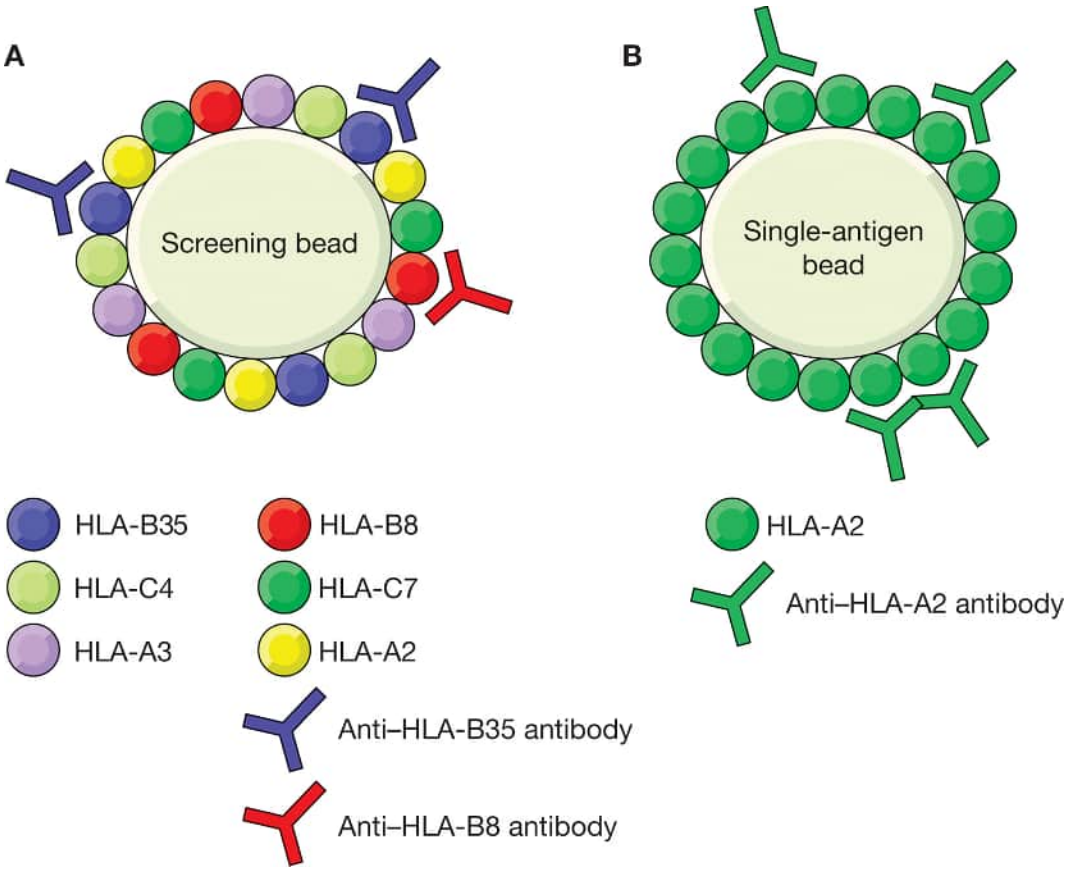


FIGURE 8.6 Solid-phase human leukocyte antigen (HLA) antibody detection methods. A. Screening/phenotype beads: Microspheres are coated with two haplotypes of HLA class I or class II antigens. Here, the HLA-A3, HLA-B35, HLA-C4 and HLA-A2, HLA-B8, HLA-C7 haplotypes are isolated from the surface of transformed cell lines and affixed to microspheres in their native conformation. The panel of beads is constructed from an array of cells bearing various HLA phenotypes representative of the donor pool. In this example, the bead identifies HLA antibody to B35 and B8. B. Single-antigen beads: A panel of single-antigen beads is constructed such that each bead contains one single recombinant antigen. In this example, single HLA-A2 antigen is affixed to the bead. The bead identifies HLA antibody to A2.

- To identify HLA antibodies, the patient's serum is mixed with antigen-coated beads. HLA antibodies in the serum bind the beads. The beads are then washed, and a fluoresceinated anti-IgG detection reagent is added. HLA antibody bound to the beads is identified on a Luminex analyzer. The single-antigen bead assay is shown in **Figure 8.7**.

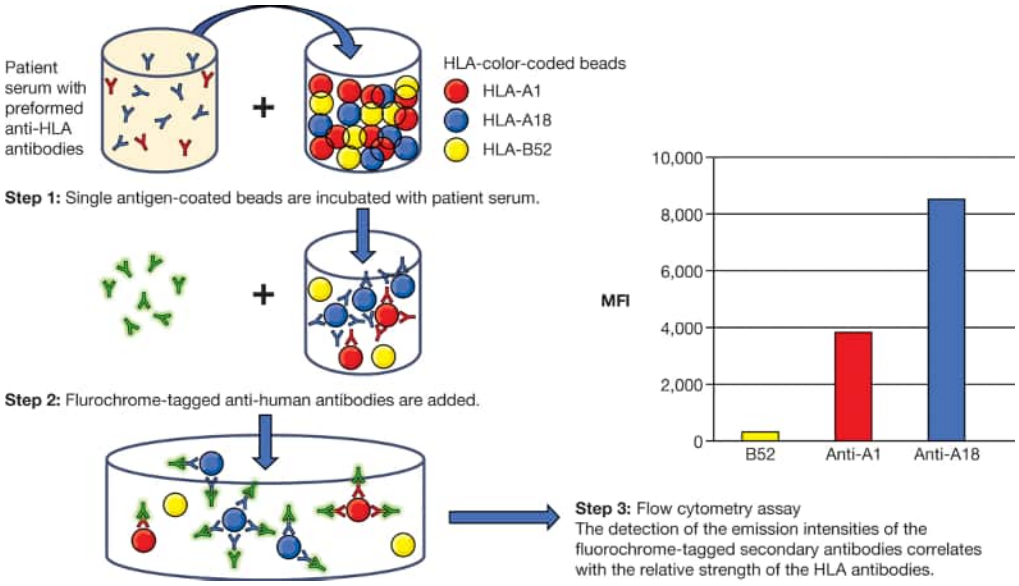


FIGURE 8.7 The single-antigen bead assay. Patient serum is mixed with single-antigen beads. Preformed antibodies in the serum bind the beads and are detected with a fluorescent detection reagent on a Luminex analyzer. The strength of the antibodies correlates quantitatively to the mean fluorescence intensity (MFI).

- The results of the assays are semiquantitative as the mean fluorescence intensity (MFI) correlates to the strength of the anti-HLA antibody but is limited to the dynamic range of the test.
- The percentage of microspheres on the panel that react with HLA antibodies in the patient's serum is referred to as percentage panel reactive antibody (%PRA).
- Both platforms have known advantages and disadvantages (discussed below). A balanced approach may be to test patient sera using both platforms to accurately establish the patient's immunologic profile.

Screening bead

Advantages

- Generally, this is less costly than the single-antigen bead test.
- HLAs are in their native conformation and can, therefore, be used to validate suspicious results identified in the single-antigen bead test due to cryptic epitopes.

Disadvantages

- Less sensitive than the single-antigen beads
- Do not identify antibodies to HLA-C, HLA-DQA, HLA-DP, or HLA-DR51/52/53
- Less specific than single-antigen beads and do not permit accurate identification of antibody specificities when the patient is broadly sensitized

Limitations

Both the single-antigen bead test and the screening beads are limited by:

- The antigens encompassed in the panel
- Identification of total IgG, and not subclass-specific ($IgG_{1\text{-}4}$), HLA antibodies
- The dynamic range of the Luminex analyzer. In the single-antigen bead test, saturation of the beads occurs around 12,000 to 15,000 MFI. Antibody strength in this range cannot be accurately assessed without modifications to the test (discussion is beyond the scope of this chapter. However, interested readers are referred to **Appendix 8.2** "Modifications of the Single-Antigen Bead Assay").

Single-antigen bead

Advantages

- Most sensitive and specific platform for identifying HLA antibodies
- Identifies antibodies to HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DR51/52/53, HLA-DQ, HLA-DQA, HLA-DP, and HLA-DPA even when the patient is very broadly sensitized

Disadvantages

- Prone to false-positive reactions due to expression of cryptic epitopes that are generated due to misfolding of the recombinant proteins
- Can generate false-negative, or falsely low, antibody strength when there are interfering factors in the sera or when the antibody is in strong excess (referred to as prozone; for interested

readers, see **Appendix 8.2**). To minimize the potential for interference, sera can be treated with reducing agents such as DTT, ethylenediaminetetraacetic acid (EDTA), or with other methods such as heat inactivation.

Unacceptable HLAs and cPRA

Unacceptable HLAs

- Unacceptable HLAs are HLAs that a transplant program is unwilling to cross. They are defined by:
  - Transplant center practice
  - The strength of the HLA antibodies present in the patient's serum as measured by solid-phase assay
  - The immunologic history of the transplant patient
- Transplant centers, in collaboration with their HLA laboratory, define unacceptable antigens by the immunologic risk and MFI (strength) of an HLA antibody to that antigen. Unacceptable antigens are then entered into UNet to prevent donor offers if the donor displays that antigen. For instance, if a patient has a strong antibody (high MFI) to HLA-B8 and HLA-B8 is entered as an unacceptable antigen into UNet, then potential donors expressing HLA-B8 will not be offered to that patient due to a predicted positive crossmatch or unacceptable risk (ie, HLA-B8 is an "unacceptable HLA").

Calculated PRA

- Entry of unacceptable antigens into UNet results in a calculated percentage PRA (cPRA) indicating the percentage of donors to which the patient is unacceptably sensitized in the UNOS donor pool. Example: A cPRA of 80% means that 80% of donors will not be acceptable to the patient.
- Since unacceptable antigens are defined by transplant center practice, patients who are listed at more than one center may have two different cPRAs.

- cPRA is calculated based on known HLA frequencies from the national UNOS donor pool; therefore, it permits a uniform measurement of sensitization for all patients across geographic regions. In 2009, cPRA replaced PRA as the metric for HLA sensitization in the UNOS kidney allocation system.
- The 2023 revised UNOS formula for cPRA incorporates HLA-DQA1, HLA-DPB1, and HLA-DPA1 loci to provide a more comprehensive assessment of sensitization. In addition, cPRA values are calculated at the allele-level antibodies, which enhances sensitivity assessment. Candidates without any unacceptable antigens reported will no longer have a cPRA score of 0%. Instead, their cPRA score will appear as **blank** or **NULL** in the system.

FYI

The cPRA calculator based on HLA frequencies found in the U.S. donor population can be found on the Organ Procurement & Transplantation Network website. Example: If a patient has antibodies against the HLA-A2 antigen (which is found in 48% of the U.S. population), and if this is the only unacceptable antigen entered into UNet, the patient's cPRA would be 48%. If a patient has antibodies against the B8 antigen (which is present in 17% of the U.S. population), and if this is the only unacceptable antigen entered into UNet, the patient's cPRA would be 17%. If a patient has antibodies against **both** the HLA-A2 and B8 antigens, the patient's cPRA would be 58% (not 48% + 17% = 65%). The resulting cPRA is less than the frequency of the HLA-A2 and B8 antigens combined because some donors express both A2 and B8 antigens (cPRA = percentage of donors expressing A2 alone + percentage of donors expressing B8 alone + percentage of donors expressing both A2 and B8).

- Patients with DSA in the serum have been shown to have poorer graft survival compared with those without DSA.

VIRTUAL CROSSMATCH

- The Clinical Laboratory Improvement Amendments (CLIA) require a crossmatch to be performed prior to transplant of a kidney.

- A virtual crossmatch is an assessment of immunologic compatibility based on the patient's alloantibody profile compared to the donor's histocompatibility antigens. Virtual crossmatching allows for risk assessment prior to transplant.
- A virtual crossmatch requires:
  - Complete molecular HLA typing of the donor (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1, HLA-DQA1, HLA-DPB1, and HLA-DPA1)
  - Molecular HLA typing of the recipient
  - The recipient's history of solid-phase anti-HLA antibody specificities
  - The recipient's history of recent sensitizing events
- At the time of virtual crossmatch, the result of a physical crossmatch can be predicted based on the strength (MFI) of preformed DSA. Accurate virtual crossmatch is important to help facilitate the import of deceased donor kidneys from across the country to reduce cold ischemia time and speed allocation. Of note, under the new kidney allocation system implemented in March 2021, kidneys will be offered first to candidates listed at transplant hospitals within 250 nautical miles of the donor hospital (ie, hospital where the kidney was recovered). Offers not accepted for any of these candidates will then be made for candidates beyond the 250 nautical mile circle (see **Chapter 9: Kidney Transplantation**).
- At the time of a virtual crossmatch, a risk assessment can also be performed. The patient's history of sensitizing events (pregnancy, transfusion, prior transplant) is essential to provide an accurate risk assessment. Donor factors, such as quality and cold ischemic time, are also considered.
- Mandatory sharing: Zero HLA-A–, HLA-B–, and HLA-DR–mismatched kidneys and kidneys for very highly sensitized candidates with a cPRA of 99% or 100% are eligible for national sharing of donor offers. Zero-mismatched kidneys are shared

because allograft survival has been shown to be superior to all other match grades.

- Acceptance or decline of the offer is made, in part, on the interpretation of a virtual crossmatch.
- **Figure 8.8** compares virtual crossmatch with physical crossmatch.

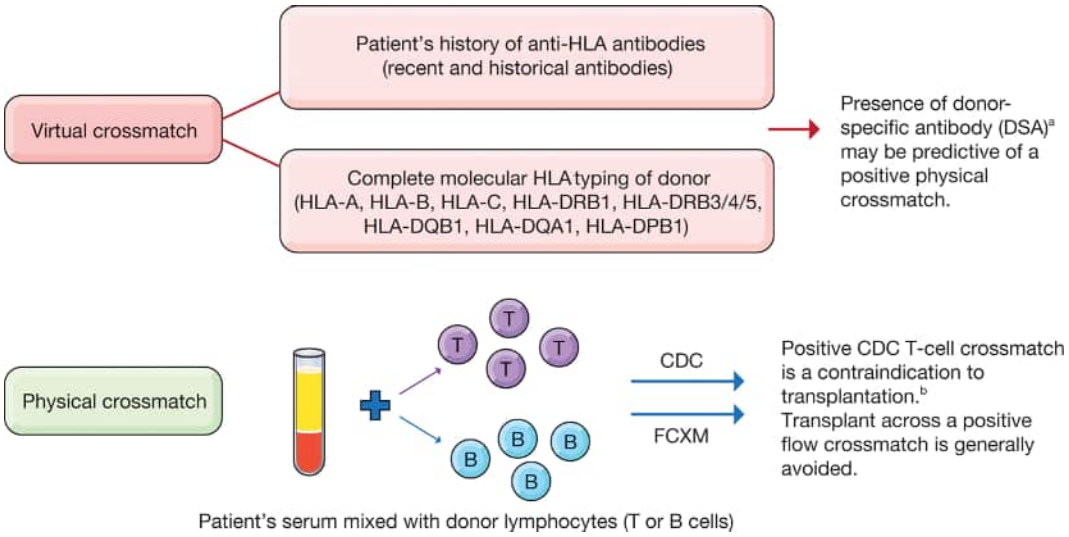

Virtual crossmatch
Patient's history of anti-HLA antibodies (recent and historical antibodies)
Complete molecular HLA typing of donor (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1, HLA-DQA1, HLA-DPB1)
Presence of donor-specific antibody (DSA)[a] may be predictive of a positive physical crossmatch.
Physical crossmatch
T
B
CDC
FCXM
Positive CDC T-cell crossmatch is a contraindication to transplantation.[b] Transplant across a positive flow crossmatch is generally avoided.
Patient's serum mixed with donor lymphocytes (T or B cells)

FIGURE 8.8 **Virtual crossmatch versus physical crossmatch.** Virtual crossmatch uses the patient's human leukocyte antigen (HLA) and immunologic history, and the donor's HLA typing, to predict the results of a physical crossmatch and provide a risk assessment prior to transplant.

Abbreviations: CDC, complement-dependent cytotoxicity; FCXM, flow cytometry crossmatch.

[a]Discussion of DSA mean fluorescence intensity (MFI) threshold for the prediction of a positive crossmatch is beyond the scope of this chapter.

[b]Transplantation in the face of a positive B-cell crossmatch and detectable DSA should be avoided.

PHYSICAL CROSSMATCH

- The physical crossmatch test can be performed prior, or perioperative, to transplantation to determine whether the patient has HLA antibody directed against a potential donor, also known as donor-specific antibody (DSA).
- Testing method is determined by center practice but generally includes the flow and/or CDC crossmatch (**Table 8.2**).

Table 8.2 Crossmatch testing methods

	Methods	Comments
Standard complement-dependent cytotoxic crossmatch	1. Recipient serum mixed with donor lymphocytes (T or B cells) 2. Complement and vital dye are added: • If recipient antidonor antibodies bind to the antigens on the donor lymphocytes, added complement will kill donor lymphocytes. • Cells that are killed are evaluated microscopically using fluorescent dyes that identify live and dead cells. Results are recorded using a semiquantitative score (eg, negative, weakly positive, strongly positive).	Detect high titer of IgG HLA antibodies that fix complement. Serum can be treated with DTT to inactivate IgM. A positive T-cell crossmatch is a contraindication to kidney transplantation. Transplant across a positive B-cell crossmatch is generally avoided.
AHG-augmented CDC crossmatch	1. Recipient serum mixed with donor lymphocytes 2. AHG reagent added 3. Complement and vital dye are added.	Adding AHG or prolonging the incubation time increases the sensitivity of the test and enhances the detection of low-titer antibodies.
Flow cytometry crossmatch (FXCM)	1. Recipient serum mixed with donor lymphocytes 2. Fluorochrome-coated anti-human IgG detection reagent is added followed by CD3 and CD19 antibodies to distinguish T and B cells. 3. Assess with flow cytometer.	Most sensitive crossmatch test Identifies anti-HLA IgG donor-specific antibodies binding to T and B lymphocytes Cells can be treated with pronase[a] to increase the sensitivity or remove Fc receptors or the CD20 molecule to produce more accurate results in some settings.

Abbreviations: AHG, anti-human globulin; CDC, complement-dependent cytotoxicity; DTT, dithiothreitol; FCXM, flow cytometry crossmatch; HLA, human leukocyte antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

[a]False-positive FCXMs are often caused by nonspecific immunoglobulin binding to Fc receptors on lymphocytes. Patients treated with antibodies such as rituximab (an anti-CD20 antibody) may also have false-positive FCXM results due to the presence of the administered antibody in their serum. Pronase is a nonspecific peptidase that preferably digests Fc receptors and other cell surface proteins (including CD20) without substantially destroying HLA molecules under certain conditions.

Complement-dependent cytotoxicity (CDC)

CDC crossmatch test is used to determine the presence of preformed high-titer IgG HLA DSA in patient serum.

Procedure

- The potential donor's lymphocytes serve as the target cells for the patient's serum.
- The CDC assay was described previously. Briefly, the patient's serum is incubated with donor T and B lymphocytes to allow HLA DSA to bind the cells. Unbound antibody is washed away, and complement and vital dye are added. Cell death is visually assessed under phase-contrast microscopy.

Interpretation

- A positive CDC crossmatch due to IgG antibodies directed against HLA class I antigens (HLA-A, HLA-B, HLA-C) is a contraindication to transplantation.
- A positive T- or B-cell CDC test in the absence of strong HLA DSA is likely due to the presence of confounding antibodies of the IgM isotype in the patient's sera. Treatment of the patient's serum with DTT inactivates IgM by eliminating the disulfide bonds required to give IgM its shape, therefore removing the confounder from the test.
- Positive B-cell CDC assays are found in the context of rituximab therapy. Rituximab is a chimeric antibody composed of a murine anti-CD20 variable region and the human IgG1k constant region. DTT treatment of the sera does not remove the binding capacity of rituximab in the CDC assay. Therefore, close communication between the clinical program and the HLA laboratory is essential for crossmatch interpretation.

- The sensitivity of the CDC assay is increased with the addition of anti-human globulin.

Flow crossmatch test (FXM)

- The FXM test is more sensitive compared to the CDC crossmatch for HLA DSA detection.
  - Antibodies directed against HLA class I of the donor can result in a positive crossmatch with both B and T cells.
  - Antibodies directed against HLA class II of the donor will only cause a positive crossmatch with B lymphocytes.
  - Therefore, a positive T-cell flow crossmatch is an indication of anti-class I DSA in the patient, whereas a positive B-cell crossmatch could be caused by either anti-class I or anti-class II DSA or both.
  - Positive B-cell flow crossmatches observed in the absence of DSA can be due to nonspecific antibody binding to Fc receptors on the surface of B cells or the presence of therapeutic biologicals such as rituximab.
  - Pronase treatment of lymphocytes prior to flow crossmatch enzymatically cleaves off Fc receptors and the similarly shaped CD20 molecule while leaving the HLA molecule intact, therefore increasing the sensitivity of the B flow crossmatch and removing confounding factors.
- The different physical crossmatch methods are summarized in **Table 8.2**.

IMMUNOLOGIC EVALUATION OF THE TRANSPLANT CANDIDATE

- Evaluation of a transplant candidate is according to center practice but generally will include molecular HLA typing of the patient and detection of HLA antibodies by solid-phase method (cell-based methods have largely been replaced by solid-phase methods).

- The patient's ABO and HLA-typing and unacceptable antigens are entered into the UNOS national kidney allocation system, with additional transplant candidate information (the UNOS kidney allocation system is discussed in **Chapter 9: Kidney Transplantation**).
- The frequency of solid-phase antibody testing and subsequent update of unacceptable antigens are according to transplant center practice. Testing frequency may differ based on the sensitization or risk category of the patient.
- The wait time until a patient begins receiving donor offers is based on a rank-ordered list generated by the UNOS match run. Kidney allocation is based on several factors, including blood type compatibility, HLA matching, dialysis wait time, proximity to the donor hospital, and sensitization to HLA. See **Chapter 9: Kidney Transplantation**.
- A very highly sensitized patient (cPRA of 99% or 100%) may receive the organ offer outside the 250 nautical mile circle.
- When a donor becomes available, the donor blood is sent to an Immunogenetics and Histocompatibility laboratory for HLA typing. The donor's HLA typing is entered into UNOS DonorNet, and a match run is performed to determine a list of potential recipients.
- A virtual crossmatch and risk assessment are performed.
  - If the patient does not display any DSA to the donor in the most recent sera, the physical crossmatch is predicted to be negative with that serum.
  - Alternatively, the patient may have preformed HLA DSA to the donor in the current sera. Based on the strength of the DSA, the physical crossmatch may be predicted to be positive. The predicted strength of the physical crossmatch, patient's clinical status and history of sensitizing events, and donor factors such as organ quality and cold ischemic time are taken into account. The patient's clinical providers will accept or decline the donor based on the collected data. If the donor is accepted, the organ is imported/shipped to the patient's transplant center,

and the patient is prepared for transplant. A physical crossmatch is generally performed using cells isolated from donor blood or tissue shipped with the organ.

- After the transplant, the patient is removed from UNeT.
- Suggested algorithm for pretransplant immune monitoring is shown in **Figure 8.9**.
- The patient is followed after transplant with solid-phase antibody detection methods to identify and longitudinally track the presence and strength of DSA that were either present prior to transplant or developed de novo post-transplant.

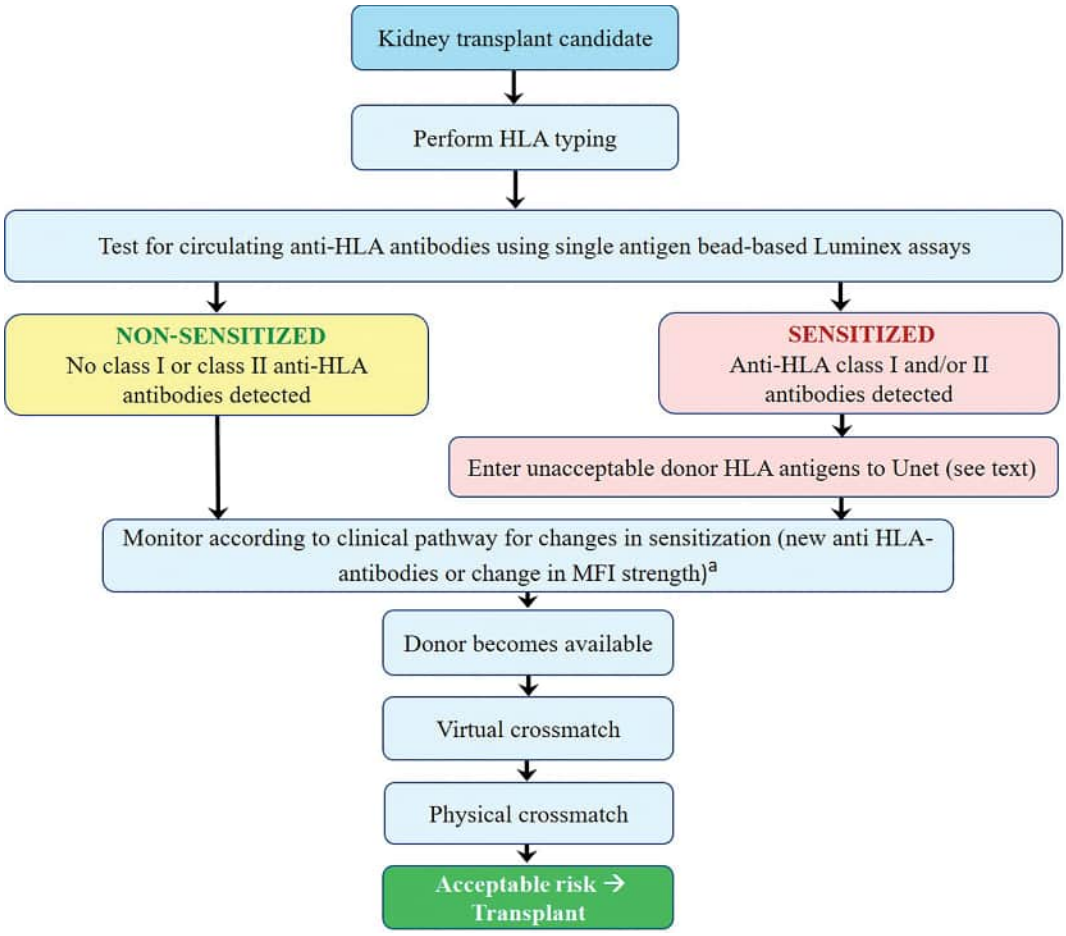

Kidney transplant candidate
Perform HLA typing
Test for circulating anti-HLA antibodies using single antigen bead-based Luminex assays
NON-SENSITIZED
No class I or class II anti-HLA antibodies detected
SENSITIZED
Anti-HLA class I and/or II antibodies detected
Enter unacceptable donor HLA antigens to Unet (see text)
Monitor according to clinical pathway for changes in sensitization (new anti HLA-antibodies or change in MFI strength)[a]
Donor becomes available
Virtual crossmatch
Physical crossmatch
Acceptable risk → Transplant

FIGURE 8.9 Suggested algorithm for pretransplant immune monitoring.

Abbreviations: HLA, human leukocyte antigen; MFI, mean fluorescence intensity.

[a]Obtain blood sample from patient every 3 months (or per center protocol) if not yet transplanted.

CHAPTER 9

Kidney Transplantation

Phuong-Thu T. Pham, Phuong-Chi T. Pham, Michelle J. Hickey, and Jonathan Zuckerman

EVALUATION OF THE POTENTIAL KIDNEY TRANSPLANT CANDIDATE

General Overview

- Kidney transplantation is the treatment of choice for suitable candidates with end-stage kidney disease (ESKD).
  - It confers survival advantage over remaining on dialysis across all ages and in both transplant recipients with diabetes and those without diabetes.
  - It offers long-term economic benefits compared to dialysis.
  - The Kidney Disease Improving Global Outcome (KDIGO) expert panel does not recommend excluding patients from kidney transplantation because of age alone. Transplant candidacy must be assessed on a case-by-case basis. In addition to a thorough medical evaluation, some centers use functional status, cognitive impairment, and frailty tools to assist in determining transplant suitability among older transplant candidates.
- The routine assessment of a kidney transplant candidate includes a thorough history and physical examination, psychosocial evaluation, and psychiatric evaluation as needed. In addition, patients should attend a patient education session and undergo a number of routine laboratory testing and imaging studies as outlined in **Table 9.1**.
- The absolute and relative contraindications to transplantation are outlined in **Table 9.2**.

- The United Network for Organ Sharing (UNOS) listing criteria for deceased donor kidney: chronic kidney disease (CKD) with glomerular filtration rate (GFR) of 20 mL/min or less or ESKD

Table 9.1 Pretransplant routine laboratory testing and imaging studies

Laboratory evaluation
Comprehensive metabolic panel
Complete blood count with platelets
Prothrombin time panel (INR and PTT)
Urinalysis and urine culture
Hepatitis B (surface Ag, IgM and IgG core Ab, and surface Ab Quant)
HCV Ab screening (if positive, check PCR confirmatory test)
HIV1/HIV2 Ag/Ab fourth generation with reflex confirmation
CMV-specific IgG
EBV-VCA IgM/EBNA1 IgG panel
RPR or VDRL (FTA-ABS confirmatory test if positive RPR or VDRL)
Iron and iron binding capacity, ferritin
Type and screen
Coccidioides IgG/IgM EIA (recommended for patients with history of valley fever or those who live in endemic areas)
Optional: serum immunofixation electrophoresis if age >60 y old (Currently, routine testing transplant candidates for MGUS is not recommended. However, practice may differ among centers.)
Special laboratory evaluation
Hypercoagulability panel in patients with history of recurrent thrombosis or spontaneous fetal losses
PSA screening for men with family history, obstructive voiding symptoms, or hematuria[a]
Serologic testing based on risk factors (endemic mycoses or travel history): coccidioides IgM and IgG Ab, histoplasma immunodiffusion Ab-Ag, strongyloides stercoralis antibody, *Leishmania* spp., *Trypanosoma cruzi* Ab, human T-cell lymphotropic virus (HTLV-1/2) Ab
Other evaluation
Electrocardiogram
Chest x-ray
PPD skin test or preferably the interferon-γ release assays (QuantiFERON-TB Gold test)
Renal ultrasound to assess for acquired cystic disease or mass
Abdominal ultrasound in diabetics to evaluate for gallstones
Cardiac evaluation (myocardial perfusion study or stress test with imaging—choice of cardiac studies differs among centers); echocardiogram to assess ejection fraction
Colonoscopy screening[b]
Pap smear and mammogram screening (appropriate for age similar to the general population)
Urologic evaluation if history of bladder/voiding dysfunction, recurrent urinary tract infections, or history of urologic abnormalities

Immunologic studies
Blood group and HLA typing
Bead-based single Ag-Ab, class I and II (see Chapter 8: Transplant Immunobiology)
Sera for crossmatch

Abbreviations: Ab, antibody; Ag, antigen; CMV, cytomegalovirus; EBNA1, Epstein-Barr nuclear antigen 1; EBV, Epstein-Barr virus; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; HCV, hepatitis C virus; HLA, human leukocyte antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; MGUS, monoclonal gammopathy of undetermined significance; PCR, polymerase chain reaction; PPD, purified protein derivative; PSA, prostate-specific antigen; PTT, partial thromboplastin time; RPR, rapid plasma regain; VCA, viral capsid antigen; VDRL, Venereal Disease Research Laboratory.

[a]Routine screening may be more harmful than protective because it does not appear to confer a survival benefit and may delay listing and decrease transplantation rates (single-center study = 3,782 men older than 18 years undergoing primary kidney transplant evaluation).

[b]Appropriate for age or at the discretion of the clinician (for a detailed discussion see Pham P-CT, Pham P-TT, eds. *Quick Guide to Kidney Transplantation*. Wolters Kluwer Inc; 2020).

Table 9.2 Contraindications to kidney transplantation

Absolute contraindications
Recent[a] or active malignancy, metastatic malignancy[b]
Untreated current infection or ongoing nonhealing ulcers
Severe irreversible extrarenal disease (eg, severe cardiovascular disease not amenable to intervention or severe pulmonary disease)
Life expectancy <2 y
Recalcitrant treatment nonadherence
Poorly controlled psychiatric illnesses
Active substance misuse
Aggressive native kidney disease[c]
Limited, irreversible rehabilitation potential
Decompensated liver cirrhosis (unless simultaneous liver-kidney transplantation)
Primary oxalosis (Consider simultaneous liver-kidney transplantation.)
Chronic severe and uncorrectable hypotension (may compromise posttransplant graft perfusion potentially leading to graft primary nonfunction)
AL amyloidosis with significant extrarenal involvement
Multiple myeloma, light chain deposition disease, heavy chain deposition disease, light chain and heavy chain deposition disease *unless* patients have received a potentially curative treatment regimen and are in stable remission (KDIGO).

Relative contraindications
Morbid obesity (center dependent)
Advanced age (center dependent—Consensus on upper age limit is lacking.)
History of multiple myeloma or plasma cell dyscrasia (assess on a case-by-case basis. Consultation with Hematology/Oncology with transplant experience strongly

recommended)
KDIGO guidelines: Smoldering multiple myeloma should not be excluded from kidney transplantation; however, significant risk of transformation into multiple myeloma should be considered and discussed with patients.

Other evaluation
ABO incompatibility[d]
Positive T- and/or B-cell crossmatch[d]

Post-percutaneous coronary intervention (PCI) candidates and candidates on anticoagulation therapy
Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel). Examples:

- Within 4 wk of coronary revascularization with balloon angioplasty
- Within 1 mo of bare metal stent placement (currently seldom used)
- Within 6-12 mo of drug-eluting stent (DES) placement, depending on clinical scenario (cardiology consult recommended)

Do not transplant patients on direct-acting oral anticoagulants (DOACs) such as apixaban or rivaroxaban, except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (KDIGO).

Abbreviations: AL amyloidosis, light chain amyloidosis; KDIGO, Kidney Disease Improving Global Outcome.

[a]See **Table 9.3**.

[b]KDIGO guidelines: We recommend not excluding candidates with a history of metastatic cancer provided that potentially curative therapy has been administered and complete remission achieved. Discussion is beyond the scope of this chapter.

[c]See **Table 9.28**—glomerular disease recurrence after transplant.

[d]Pretransplant preconditioning regimen or desensitization may allow successful transplantation across these barriers (discussion is beyond the scope of this chapter). See **Chapter 8: Transplant Immunobiology** for different crossmatch methods. Positive complement-dependent cytotoxicity crossmatch is a contraindication to transplantation. *Other options:* Paired donor exchange or kidney-paired donation (KPD) at the internal (involving one single-transplant center), regional (involving multiple transplant centers within close geographical or system networks), or national level (via the National Kidney Registry).

- Transplant candidates with a history of malignancies:
  - Active malignancy is an absolute contraindication to kidney transplantation except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤6), incidental renal tumor (≤1 cm), or superficial nonmelanoma skin cancer (KDIGO).

- Suggested tumor-free waiting period for common malignancies is shown in **Table 9.3**.
- Hematology/Oncology referral is recommended.

- Disease recurrence after transplantation: Patients should be informed of the risk of disease recurrence after transplantation and the risk of graft loss associated with disease recurrence (discussed under Posttransplant Noninfectious Complications).

Table 9.3 Tumor-free waiting period for common pretransplant malignancies

No waiting time
Long-standing history of MGUS. Consult Hematology-Oncology for newly diagnosed disease.

No waiting time if cure at the time of transplant (KDIGO)
Nonmetastatic basal cell and squamous cell carcinoma (SCC) of the skin; melanoma in situ; small renal cell carcinoma (<3 cm); prostate cancer (Gleason score ≤6); carcinoma in situ (ductal carcinoma in situ [DCIS], cervical, others); thyroid cancer (follicular/papillary <2 cm of low-grade histology); superficial bladder cancer

Waiting time varies with staging, tumor size
Per 2020 KDIGO unless otherwise specified. Note: KDIGO and AST guidelines may differ.

Prostate cancer
- Gleason score ≤6: no wait time
- Gleason 7: at least 2 y; Gleason 8-10: at least 5 y
- Metastatic castration resistant: NOT a candidate (AST consensus statement)

Renal cell carcinoma
- Incidental renal tumor (<3 cm): no wait time
- Early: at least 2 y; large and invasive: at least 5 y
- Any T, node positive, metastatic disease: NOT a candidate (AST consensus statement)

Breast cancer (2019 AST consensus statement)
- Stage 1 (DCIS): no wait time
- Stage II: 1-2 y no evidence of disease; Stage III: 3-5 y no evidence of disease
- Stage IV: not a candidate

Skin squamous cell carcinoma[a-c]
- Low-risk SCC: surgical excision with clear margins or Mohs surgery, no waiting time
- High-risk SCC: no perineural invasion, surgical excision with clear margins or Mohs surgery, 2 y waiting time
- High-risk SCC with perineural invasion: surgical excision with clear margins or Mohs surgery ± adjuvant radiation therapy and waiting time of 5 y
- High-risk SCC with local nodal disease: surgical excision, lymph node dissection, adjuvant radiation therapy, and 5 y waiting time

Melanoma[a-c]

- In situ: wide excision and no waiting time
- Stage Ia: wide local excision and 2 y waiting time
- Stage Ib/IIa: wide local excision and ± sentinel lymph node biopsy and 2-5 y waiting time
- Stage IIb/IIc: wide local excision and ± sentinel lymph node biopsy and 5 y waiting time
- Stage III or IV: not a transplant candidate

Colorectal cancer: Dukes A/B: at least 2 y; Duke C: 2-5 y; Duke D: at least 5 y
Bladder cancer (AST consensus statement)

- Nonmuscle invasive: 6 mo-2 y; muscle-invasive, post-radical cystectomy: 2 y
- Muscle-invasive, post-chemoradiation: NOT a candidate

Uterine cancer: localized: at least 2 y; invasive: at least 5 y
Cervical cancer: localized: at least 2 y; invasive: at least 5 y
Posttransplantation lymphoproliferative disorder (PTLD): nodal: at least 2 y; extranodal and cerebral: at least 5 y

NB: Certain cancers may recur despite a tumor-free waiting period.

Abbreviations: AST, American Society of Transplantation; KDIGO, Kidney Disease Improving Global Outcome; MGUS, monoclonal gammopathy of undetermined significance.

[a]Oncology consultation is recommended.

[b]Dermatology consultation is recommended.

[c]From Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant*. 2017;17(10):2509-2530.

Candidates With Preexisting Infectious Diseases

Hepatitis B

Diagnostic testing for hepatitis B virus (HBV) is shown in **Table 9.4**. Patients with hepatitis B surface antigen (HBsAg) positive with or without evidence of active viral replication should be referred to hepatology (the latter as assessed by the detection of HBV DNA by reverse transcriptase polymerase chain reaction [PCR]).

Table 9.4 Diagnostic tests for hepatitis B and C

Hepatitis type	Diagnostic tests and interpretation
Hepatitis B	• Hepatitis B surface antigen (HBsAg): HBV infection • IgM antibody to hepatitis core antigen (IgM anti-HBc): acute or recent HBV infection

Hepatitis type	Diagnostic tests and interpretation
	• IgG antibody to hepatitis B core antigen (IgG anti-HBc): chronic or remote HBV infection • Antibody to hepatitis B surface antigen (HBsAb): immunity to HBV (prior infection or through vaccination) • Hepatitis B e-antigen (HBeAg): active viral replication • HBV DNA (HBV viremia): active viral replication

Hepatitis C	• Anti-HCV: used for initial screening. The third-generation ELISA 3.0 has excellent sensitivity and specificity.
	• Nucleic acid test for detection of HCV RNA (qualitative vs quantitative)
	  • HCV qualitative
	  • More sensitive than quantitative test
	  • Used to confirm HCV infection in anti-HCV positive patients
	  • Useful in immunocompromised patients (patients on dialysis, transplant recipients)
	  • HCV quantitative
	  • More reproducible than qualitative tests
	  • Used to assess viral load
	  • Useful in monitoring response to therapy
	• HCV genotyping: may help in treatment decisions and predict response to treatment (The advent of pan-genotypic DAA regimen has revolutionized the treatment outcomes for HCV infection, irrespective of genotype.)

Abbreviations: DAA, direct-acting antiviral; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

Assessment of severity of liver disease

- Liver enzymes may be spuriously normal in patients with CKD despite advanced liver disease.
- Noninvasive diagnostic tools including transient, shear wave, and magnetic resonance (MR) elastography are increasingly being used in lieu of a liver biopsy to assess the severity of chronic liver disease. However, if noninvasive testing cannot definitively exclude cirrhosis or if there is clinical concern for the presence of cirrhosis, transjugular liver biopsy remains the gold standard.

Hepatocellular carcinoma screening every 6 months with the following studies is recommended:

- Abdominal ultrasound

- α-Fetoprotein

Transplant considerations

- Kidney-alone transplantation is acceptable after sustained viral response in patients with minimal to moderate chronic fibrosis (stages I-III) or compensated liver cirrhosis (defined as absence or mild portal hypertension [HTN] with hepatic portal venous gradient <10 mm Hg). Hepatology consult is recommended.
- Patients with decompensated liver disease should be referred for simultaneous liver-kidney transplantation (SLKT).

Antiviral therapy considerations

- Transplant candidates with active HBV replication (ie, detectable HBV DNA): Initiate antiviral therapy pretransplant.
- Transplant recipients with HBV infection (ie, positive HBeAg or HBsAg): All patients should be placed on antiviral therapy after transplantation to avoid HBV reactivation and progression of liver disease associated with the use of immunosuppressive therapy.
- The authors advocate antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation.

Hepatitis C

Diagnostic testing for hepatitis C virus (HCV) is shown in **Table 9.4**.

- Serologic testing is the initial screening tool for HCV infection.
- The third-generation enzyme-linked immunosorbent assay (ELISA 3.0) has excellent sensitivity and specificity even for patients with CKD.
- Confirmation of chronic HCV infection requires detection of HCV RNA by reverse transcriptase PCR.
- All patients should be referred to hepatology.

Assessment of severity of liver disease is similar to that discussed earlier for hepatitis B.

Transplant considerations

- Kidney-alone transplantation is acceptable with HCV treatment in patients with minimal to moderate chronic fibrosis (stages I-III) or

compensated liver cirrhosis (absence or mild portal HTN with hepatic portal venous gradient <10 mm Hg). Hepatology consult is recommended.

- Patients with decompensated liver disease should be referred for SLKT.

Antiviral therapy considerations

- The advent of highly effective, pan-genotypic, direct-acting antiviral (DAA) agents and the now wide availability of oral combination agents targeting different stages of the HCV replicative cycle can potentially eradicate HCV infection in kidney transplant candidates and recipients.
- Active viral replication at the time of transplant has been shown to be associated with a higher incidence of long-term clinical liver disease and worse allograft function and graft survival compared with HCV-positive recipients with persistently negative viremia. Pretransplant treatment of hepatitis C can halt the progression of liver disease.
- For HCV-positive transplant candidates without a living donor, consider delaying DAA therapy until after transplant, as waiting times are significantly shorter for deceased HCV-positive donors. Nonetheless, among those with advanced fibrosis, treatment before transplant is recommended by experts in the field. In those with mild to moderate fibrosis, treatment can be deferred until after transplant.
- Kidneys from hepatitis C–positive donors may be offered to hepatitis C–positive transplant candidates (who are viremic) who have consented to receive such kidney (informed consent should preferably be obtained at the time of pretransplant evaluation).
- Hepatitis C–positive donors to hepatitis C–negative candidates and preemptive therapy with DAA agents after transplantation is a potential therapeutic option for waitlisted transplant candidates who consent to receive such kidney. Discussion is beyond the scope of this chapter.

Human immunodeficiency virus (HIV)

Kidney transplantation in patients with stable disease: Highly active antiretroviral therapy (HAART) regimen has allowed successful transplantation of patients with stable HIV, defined as:

- Undetectable HIV viral load
- CD4 lymphocyte count of greater than 200/mm^2
- Absence of opportunistic infections in the previous year

Transplant considerations

- Specific recommendations may vary from center to center.
- Clinicians should remain vigilant to significant drug-drug interactions between HAART and immunosuppressive drugs metabolized by CYP450 such as the calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors (See **Table 9.13** "Drug-drug and drug-food interactions").

Latent tuberculosis (TB)

- All potential kidney transplant candidates should undergo a purified protein derivative (PPD) skin test or preferably the interferon-γ (IFN-γ) release assays (QuantiFERON-TB Gold test) because the latter has lower false-positive rates associated with prior Bacille Calmette-Guérin (BCG) vaccine.
- A positive skin test or IFN-γ released assay result or a prior history of TB mandates further evaluation to rule out active disease.
- Obtain chest x-ray (part of routine pretransplant workup).
- Isoniazid (INH) prophylaxis for a total of 9 months is recommended for those with evidence of latent TB.
- Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation.

LIVING DONOR EVALUATION

Living Donor Options

- Living kidney transplantation may include living-related, living-unrelated, kidney-paired donation, paired kidney chain donation, voucher donation, or altruistic kidney donation.

- The Declaration of Istanbul on organ trafficking and transplant tourism and the World Health Organization (WHO) prohibit and condemn the exploitation of vulnerable living donors (defined as individuals with limited literacy skills or those facing economic hardship, undocumented immigrants, and political or economic refugees).

Kidney-paired donation (KPD), paired kidney chain donation

- Approximately 30% of potential living donors are incompatible with their recipients due to blood group incompatibility or the presence of preformed donor-specific human leukocyte antigen (HLA) antibody, or both.
- KPD is a program in which an incompatible donor-recipient pair is swapped with another incompatible donor-recipient pair. A number of transplant centers in the United States offer KPD and/or desensitization protocols to such willing but incompatible healthy donor-recipient pairs. Sometimes these "swaps" may include multiple pairs.
- Paired kidney chain donation (formerly known as domino-paired kidney donation or never-ending altruistic donation [NEAD]). The nondirected donor donates a kidney to a compatible recipient who has an intended but incompatible living donor. The recipient's incompatible living donor will, in turn, donate their kidney to the next incompatible pair, generating a domino effect. The chain can terminate when the final donor donates to a recipient on the deceased donor's waiting list. Alternatively, the final donor can wait until a suitable match is found with a new incompatible pair. As such, the final donor becomes a bridge donor to continue the chain until no match can be identified through paired kidney donation, and the final donor's kidney is directed to a recipient on the deceased donor waitlist.

Voucher donation

- In a voucher donation program, the donor donates a kidney at a time that is optimal for the donor, whereas the intended recipient is

not yet in need of a transplant or may never need a transplant. Example: A 66-year-old grandmother can donate a kidney to a nondirected recipient now to allow her 7-year-old grandson with CKD to receive priority for a future living donor kidney transplant if needed later in life.

- Advantages: Vouchers for future kidney transplantation overcome "chronologic incompatibility" between living donors and recipients.

Altruistic kidney donation refers to the act of donating without having an intended recipient (aka nondirected or Good Samaritan donor).

General Assessment

- Complete history and physical examination, and psychosocial assessment.
- Psychosocial assessment by the transplant center psychiatrist or social worker is recommended to evaluate for any significant psychiatric problem and any possibility of coercion. The presence of either of these would preclude donation.
- Transplant programs are required to appoint an independent living donor advocate (ILDA) to support potential donors throughout the process and to promote donor understanding of the informed consent including the risks and benefits of donation. The ILDA can be a social worker, nurse, psychologist, or physician (in many programs the social worker functions as the ILDA).
- Suggested routine evaluation and optional testing are listed in **Table 9.5**.
- Absolute and relative contraindications to living kidney donation are listed in **Table 9.6**.

Table 9.5 Suggested routine evaluation and optional testing

Laboratory tests
ABO blood group, HLA tissue typing, crossmatch testing
Urinalysis (with reflex microscopic) and urine culture
24-h urine for albumin, protein,[a] and creatinine clearance (or GFR by nuclear medicine test). Some centers measure GFR using the 2021 CKD-EPI creatinine-cystatin C equation.
CBC with platelets, INR, and PTT

Comprehensive metabolic panel (electrolytes, liver function, uric acid)
Hemoglobin A_{1C}, fasting lipid profile

Serologies[b]: hepatitis B (surface Ag and Ab, IgM and IgG core Ab), HCV Ab, HCV RNA quantitative PCR, HIV1/HIV2 fourth generation with reflex, CMV, EBV, HSV, West Nile antibodies (IgG and IgM), RPR or VDRL (FTA-ABS confirmatory test if positive RPR or VDRL), *Strongyloides stercoralis* antibodies
QuantiFERON-TB Gold test (preferred over PPD skin test)
Geographic residence or environmental exposure that may require additional testing: coccidioidomycosis, schistosomiasis, malaria, HHV-8, HHV-6, *Trypanosoma cruzi*
Women <53-55 y: human chorionic gonadotropin quantitative pregnancy test
Prospective donors >60 y: serum protein electrophoresis and immunofixation
African Americans: hemoglobin electrophoresis (to rule out sickle cell trait)

Other tests
Electrocardiogram; chest x-ray
Pap smear appropriate for age similar to the general population
Mammogram appropriate for age similar to the general population
Renal imaging: CT angiogram, spiral CT, or magnetic resonance angiogram

Further testing depending on age, history, abnormal laboratory findings, family history
Cardiac screening: exercise treadmill or nuclear medicine stress test, echocardiogram
Colonoscopy for prospective donors ≥50 y
24-h ambulatory blood pressure monitoring
Renal biopsy
Cystoscopy
Screening for hypercoagulability
Oral glucose tolerance test in patients at risk for or with family history of diabetes
PSA screening for men with family history at the discretion of the clinician
African Americans: screening for APOL L1 G1/G2 mutation (see text)

NB: Routine evaluation and optional testing may vary among centers.

Abbreviations: Ab, antibody; Ag, antigen; CBC, complete blood count; CKD-EPI, chronic kidney disease epidemiology; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; FTA-ABS, fluorescent treponemal antibody absorption; GFR, glomerular filtration rate; HCV, hepatitis C virus; HHV, human herpes virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; PCR, polymerase chain reaction; PPD, purified protein derivative; PSA, prostate-specific antigen; PTT, partial thromboplastin time; RPR, rapid plasma regain; VDRL, Venereal Disease Research Laboratory.

[a]KDIGO (Kidney Disease Improving Global Outcome) guidelines recommend that donor proteinuria should be measured as albuminuria, not total urine protein. In the authors' opinion, both urine albumin and total protein should be measured because the former does not detect light-chain immunoglobulins.

[b]All potential living donors should be tested as closely as possible but within 28 days prior to, organ recovery for: HIV RNA by nucleic acid testing (NAT) and anti-HIV testing; HBV (hepatitis B virus) NAT, total anti-HBc (anti-hepatitis B core), and HBsAg (hepatitis B surface antigen) testing; and HCV NAT and anti-HCV testing.

Table 9.6 Absolute and relative contraindications to living kidney donation

Absolute contraindications (at most transplant centers)	Relative contraindications
• Evidence of kidney disease (GFR <80 mL/min/1.73 m^2, and/or microalbuminuria ≥30 mg/24 h [or equivalent]) (See relative contraindication regarding KDIGO guidelines.) • Significant renal or urologic abnormalities • Transmissible infectious disease (HIV[a], hepatitis B infection, hepatitis C infection[b], *Trypanosoma cruzi* infection [Chagas disease][c]) • Active malignancy or incompletely treated malignancy that either requires treatment other than surveillance or has more than minimal known risk of transmission.[d] • Chronic illness that places patient at significant risk of undergoing surgery • Poorly controlled psychiatric illness or active substance misuse • Cognitive deficit • Current pregnancy • Hypertension (HTN; clinically significant HTN, see text) • Type 1 DM (absolute contraindication), type 2 DM (see text) • Recurrent nephrolithiasis or bilateral stones • History of thrombotic disorders with risk factors for future events or inherited hypercoagulable states (eg, the presence of anticoagulant or anticardiolipin antibody, Factor V Leiden, or prothrombin gene mutation FII-20210) • High suspicion for covert coercion • BMI >30-35 kg/m^2 (center dependent) • Urologic abnormalities of donor kidney	• Age <18 y (seldom performed) or >70 y (need to evaluate on a case-by-case basis) • Borderline or mild HTN (should be evaluated on a case-by-case basis) • Borderline urinary abnormalities in the absence of renal function impairment • Single prior episode of kidney stone without evidence of secondary risk (see **Table 9.7**) • Obesity (center dependent, generally defined as body mass index [BMI] >30 kg/m^2) • Metabolic syndrome and fatty liver (must resolve or demonstrate significant improvement through lifestyle changes before donation) • Young donor with risk factors for future development of diabetes mellitus • Jehovah's Witness • African Americans with two mutated alleles of APOL1 G1/G2 (see text) • Sickle cell trait (Sickle cell trait is considered an absolute contraindication to living donation at some centers.) • Cigarette smokers (must stop at least 4 wk prior to surgery to decrease pulmonary complications). At some centers, current cigarette smoking is considered a contraindication to donation. • KDIGO guidelines for GFR between 60 and 80 mL/min/1.73 m^2 and/or albumin excretion rate (AER) between 30 and 100 mg/d: Decision should be individualized based on demographic and health profile in relation to the transplant center's acceptance risk threshold.

DM, diabetes mellitus; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcome; OPTN, Organ Procurement Transplant Network.

NB: Absolute and relative contraindications may vary among centers.

[a]Exception: In 2015, the OPTN created a variance in which HIV-positive organs are considered for HIV-positive candidates at transplant hospitals who have received Institutional Review Board (IRB) approval consistent with research criteria published by the National Institutes of Health and OPTN approval. Interested readers are referred to OPTN policies, procedures implemented to support HOPE Act on the United Network for Organ Sharing (UNOS) website. The first living donor HIV-to-HIV kidney transplant was performed in the United States in March 2019 (HIV Organ Policy Equity [HOPE] in Action is an ongoing prospective multicenter, clinical trial of HIV-to-HIV deceased donor kidney transplantation).

[b]Kidneys from hepatitis C–positive donors may be offered to hepatitis C–positive transplant candidates (who are viremic) who have consented to receive such kidneys.

[c]UNOS policy: If transplantation from an infected donor is planned, recipients should receive specific information regarding the risk of transmission and limited data regarding the risk, especially pertaining to live donors, posttransplantation monitoring, and potential toxicities associated with treatment for Chagas disease. Detailed discussion is beyond the scope of this chapter.

[d]Policy revision in 2016 permits transplantation of organs removed as part of treatment for an individual's health condition (eg, transplanting living donor kidney with small, T1a, renal cell carcinoma. Should be evaluated on a case-by-case basis. Discussion is beyond the scope of this chapter.

Table 9.7 Prospective donors with history of kidney stones

Kidney donation acceptable	Contraindications to donation if one or more of the following risk factors are present

• Distant history of stone (>10 y) without metabolic abnormalities associated with stone formation (eg, hypercalcemia, hyperuricemia, hyperoxaluria, hypocitraturia, or metabolic acidosis)
• Current asymptomatic single stone if:
  • Stone is <1.5 cm or potentially ureteroscopically removable from explanted donor kidney (before transplantation), AND
  • Further evaluation must reveal no evidence of metabolic abnormalities, urinary tract infection, or nephrocalcinosis.
• Single stone episode associated with treated primary hyperparathyroidism and normocalcemia does not necessarily preclude donation (must evaluate on a case-by-case basis).
	• Cystinuria
	• Sarcoidosis
	• History of struvite stones
	• Inflammatory bowel disease
	• Evidence of nephrocalcinosis
	• Primary or enteric hyperoxaluria
	• History of bilateral stones, multiple stones, recurrent stones despite preventive therapy

Kidney donation acceptable	Contraindications to donation if one or more of the following risk factors are present
AST Living Donor Community of Practice Guideline The following are considered acceptable for donation: • Incidental stones (<2-3 mm) and negative metabolic stone evaluation (Donor should be left with stone-free kidney.) • Candidates with a distant history of a single passed stone without recurrent stone on current imaging and negative metabolic evaluation[a]	

Abbreviations: AST, American Society of Transplantation.

[a]An online calculator that may be used to predict stone recurrence is available at Calculate by QxMD: ROKS—Recurrence of Kidney Stone (2014).

Evaluation for Specific Conditions

Diabetes mellitus

American Society of Transplantation (AST) Living Donor Community of Practice (opinion based)

- Prediabetes increases future risk for diabetes-associated kidney disease in the donor.
- Potential donors with diabetes mellitus (DM) are excluded from donation per UNOS.
- Potential donors with prediabetes need to make lifestyle changes including diet change and increased exercise and weight loss to normalize glucose metabolism and reduce future diabetes risk. May donate if glucose metabolism normalizes after lifestyle changes

2017 KDIGO inclusion and exclusion criteria for donation

- Donor candidates with type 1 diabetes should not donate.
- Donor candidates with prediabetes or type 2 diabetes
  - Decision for kidney donation should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

- Donor candidates should be counseled that their condition may progress over time and may lead to end-organ complications.

Hypertension

AST Living Donor Community of Practice (opinion based)

- Medical evaluation of potential donors suspected to have HTN should include:
  - Ambulatory blood pressure (BP) monitoring
  - Evaluation of end-organ damage (eg, retinal evaluation, echocardiogram to assess for left ventricular hypertrophy)
- White donors with HTN should not be precluded from donation if the following criteria are met:
  - Age above 50 years
  - HTN is well controlled with one antihypertensive agent.
  - GFR of greater than 80 mL/min/1.73 m^2 and urine albumin excretion of less than 30 mg/d (Amsterdam guidelines)
  - Candidates are reliable and agree to long-term follow-up.
- Living donation among young African Americans with HTN is generally discouraged due to their possible genetic predisposition to ESKD and higher rates of ESKD.
- Younger candidates with HTN and a family history of kidney disease may not donate.

2017 KDIGO Clinical Practice Guidelines

- Donor candidates with HTN that can be controlled to a systolic BP of less than 140 mm Hg and a diastolic BP of less than 90 mm Hg using one or two antihypertensive agents, who do not have evidence of end-organ damage, may be acceptable for donation.
- Donor candidates should be informed that:
  - BP may rise with aging.
  - Donation may accelerate the rise in BP and the need for antihypertensive treatment over that expected with normal aging and among those with high-normal BP before donation (particularly in African Americans).

- Antihypertensive medication is more likely to be prescribed after donation.

Donor with a history of nephrolithiasis **(see Table 9.7)**

Hereditary kidney disease

Autosomal dominant polycystic kidney disease (APKD)

- Most commonly encountered hereditary kidney disease
- Diagnostic criteria are age and genotype dependent (ie, polycystic kidney disease 1 or 2 [PKD1 or PKD2]).
  - PKD1
    - Younger than 30 years: one or more cysts in each kidney or two or more cysts in one kidney
    - 30 to 59 years of age: two or more cysts in each kidney
    - 60 years of age: four or more cysts in each kidney
  - PKD2
    - May present later in life. The use of PKD1 diagnostic criteria may lead to false-negative results. In asymptomatic patients from families with known and well-characterized pathogenic mutations in the *PKD2* locus, genetic testing is more definitive than ultrasound.
  - At risk but unknown familial genotype
    - Between 15 and 39 years of age: at least three unilateral or bilateral kidney cysts
    - 40 to 59 years of age: two or more cysts in each kidney
    - 60 years or older: four or more cysts in each kidney
- Ultrasound screening is acceptable for prospective donors older than 30 years.
- If ultrasound is equivocal, or the prospective donor is 18 to 30 years of age, consider genetic testing or magnetic resonance imaging (MRI). Of note, genetic testing is only useful in screening donors when the mutation in the affected family member is successfully identified.

- MRI-based criteria for disease exclusion in at-risk individuals younger than 40 years. The finding of less than five cysts is sufficient for disease exclusion.
- For prospective donors with positive family history and age below 30 years, direct mutation analysis for PKD1 and PKD2 is required at some centers.
- Targeted gene panels for known mutations associated with hereditary kidney diseases are being developed and validated. Such development may be useful for the evaluation of living-related-donor candidates.

Apolipoprotein L1 (APOL1) gene mutations

- Two risk allele mutations (homozygous G1/G1, homozygous G2/G2, or compound heterozygous G1/G2) are found in approximately 13% to 32% of African Americans and are associated with an increased risk of nondiabetic glomerulosclerosis, focal and segmental glomerulosclerosis (FSGS), and more rapid CKD progression compared with their non-black counterparts. African American kidney donors are at greater risk of developing ESKD than their European American counterparts. The UNOS data demonstrated that the risk of ESKD 15 years postdonation was 74.4 per 10,000 African American donors compared with 22.7 per 10,000 European American donors.
- Donor candidates with two APOL1 risk alleles should be informed of the increased lifetime risk of kidney failure but the precise kidney failure risk after donation cannot currently be quantified. In a small series of 19 living donors with 2 APOL*1* kidney-risk variants, 2 (11%) developed ESKD at a median of 12 years after donation.
- Living donor candidates should be informed that not all individuals carrying 2 APOL*1* kidney-risk variants develop kidney disease and "second hits" are required for deterioration in kidney function. Currently, the nature of second hits beyond certain viral infections is unknown.
- AST's Live Donor Community of Practice Expert Opinion:

    - African American living donor candidates with risk factors for the development of ESKD such as young age (<44 years), male gender, history of smoking, obesity (body mass index >30kg/m^2), HTN, low to normal estimated glomerular filtration rate (eGFR) (90-99mL/min/1.73 m^2), and a family history of ESKD, HTN, or diabetes in a first-degree relative may be considered for APOL1 genetic testing.
    - Genetic testing should only be offered after appropriate counseling.
- Renal allografts from living and deceased donors with two risk alleles for APOL1 variants have an increased risk for rejection and transplant failure. Similar to native kidney disease, a second insult may be required to develop allograft failure.

NOTE

AST's Live Donor Community of Practice Expert Opinion: Genetic counseling by a transplant nephrologist or a member of the transplant team should be performed before genetic testing and again after obtaining results. Isolated findings of two APOL1 risk variants should not be sufficient to rule out a candidate. In the presence of a high-risk genotype, the decision to donate should be handled through shared decision-making between the transplant team and potential donor. To protect the donor's privacy, the transplant team should not reveal the donor candidate's APOL1 genotype to the recipient.

Pregnancy

- Desire to become pregnant is not a contraindication to donation. However, prospective female donors of childbearing age should be informed to avoid becoming pregnant from the time of approval for donation (or preferably from the time of donor evaluation to the time of recovery after nephrectomy).
- Female donor candidates should not donate while pregnant.
- Evaluating for donation 6 months postpartum is reasonable.
- Prospective female donor candidates of childbearing age should be informed that kidney donation may increase the risk of gestational HTN and preeclampsia (11% vs 5% among healthy nondonors counterparts).

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- Women with a prior history of hypertensive disorders of pregnancy (eg, gestational HTN, preeclampsia, or eclampsia) may be acceptable for donation if their long-term postdonation risks are acceptable.
- Women with childbearing potential who proceed with donation should be counseled on how to reduce the risk of complications in future pregnancies (close follow-up with a nephrologist during pregnancy is advisable).

Donor Safety and Long-Term Renal Function

Surgical risks

- Kidney donor surgery has a 0.007% mortality rate (ie, for every 100,000 living donor surgeries, 7 donors die). Source: National Kidney Registry.
- Surgical mortality within 90 days of live kidney donation: 0.031% (or 3.1/10,000 donors). Source: UNOS database consisting of 80,347 live kidney donors.
- Donors who are obese are at increased risk for surgical morbidity.

Mortality risks

- No apparent adverse effect on life expectancy
- However, living kidney donors who are obese might be at increased risk of long-term mortality (see **Appendix A9.1**).

Long-term risks on kidney function

- Despite the loss of 50% renal mass, unilateral nephrectomy only reduces renal function by approximately 20% to 30% at long-term follow-up because of compensatory hyperfiltration. The degree of compensation is determined by age-related reserve.
- Systematic review, meta-analysis, meta-regression study (n >5,000 donors from 27 countries): Kidney donation resulted in small increases in urinary albumin, which increased with time after donation. An initial decrement in GFR was not followed by accelerated loss over the subsequent 15 years.

- One-third of healthy donors will have eGFR of less than 60 mL/min/1.73 m^2. However, the fall in eGFR usually does not decrease with time beyond the rate associated with natural aging (see **Appendix A9.2**).
- Although there is an increased relative risk (RR) of ESKD after kidney donation, the absolute risk for ESKD is still less than 0.5% at 15 years and 0.9% for lifetime risk compared to 3.2% for the general population.
- The Organ Procurement Transplant Network (OPTN) policy requires informing donor candidates that the risk of ESKD after donation may exceed that of healthy nondonors with medical characteristics similar to living kidney donors.
- Risk for ESKD: Black race, male sex, greater body mass index, donors with first-degree biologic relationship to the recipient (data source: OPTN database with ESKD ascertained via Centers for Medicare and Medicaid Services linkage; *n* >130,000 living kidney donors)
- African Americans have higher rates of developing postdonation CKD due to HTN and use of antihypertensive medication compared to white donors.

Other long-term risks

May increase the risk of HTN regardless of race (Black or White) (see **Appendix A9.3**), hyperuricemia, gout, hyperthyroidism, and preeclampsia (systematic review and meta-analysis of 52 studies involving more than 110,000 living kidney donors with follow-up of 1-24 years showed that the RR for preeclampsia in female donors was 2-fold higher among living donors compared with their non-donor counterparts, with an estimated incidence rate of nearly 6 cases per 100 pregnancies)

FYI

For interested readers, a calculator to assess the risk of developing kidney disease in the absence of donation can be found online at Transplant Models: ESKD (end stage kidney disease) Risk Tool for Kidney Door Candidates. This risk model is intended for low-risk

adults considering living donation in the United States. **This risk calculator should not replace clinical judgment.**

KIDNEY ALLOCATION SYSTEM

UNOS Listing Criteria

- CKD with eGFR of 20 mL/min or less *or*
- Currently receiving kidney replacement therapy

Kidney Donor Profile Index (KDPI)

- Deceased donor kidneys are given a KDPI value ranging from 0% to 100% based on longevity-matching concepts. Ten donor characteristics used to calculate KDPI:
  - Donor age
  - Height
  - Weight
  - Ethnicity
  - History of HTN
  - History of diabetes
  - Serum creatinine (SCr)
  - Cause of death
  - Hepatitis C status
  - Donation after circulatory death status
- Lower KDPI values are associated with longer-estimated function, whereas higher KDPI values are associated with shorter-estimated function (eg, a kidney with KDPI of 20% is expected to have longer longevity than 80% of recovered kidneys).

Factors Determining Kidney Allocation

Waiting time

- Preregistration dialysis time allows transplant candidates to gain waiting time upon listing (eg, patient who has been on dialysis for 5

years prior to UNOS registration will have 5 years of waiting time upon listing).

- Candidates not yet on dialysis at the time of registration will still begin to accrue waiting time once they are registered on the waiting list.

Distance-based allocation

- Kidneys will be offered first to candidates listed at transplant hospitals within 250 nautical miles of the donor hospital (250 nautical mile circle). Offers not accepted for any of these candidates will then be made for candidates beyond the 250 nautical mile distance.
- Candidates will also receive proximity points based on the distance between their transplant program and the donor hospital. The point assignment will be highest for those closest to the donor hospital and will decrease as the distance increases.

Degrees of allosensitization (cPRA [calculated panel reactive antibody] ≥20%)

- Higher cPRA scores indicate increasing difficulty in getting a kidney with a negative or acceptable crossmatch. (cPRA is discussed in **Chapter 8: Transplant Immunobiology**.)
- Prioritization points will be assigned based on a sliding scale, beginning with a cPRA score of 20%. Examples:
  - Candidates with a cPRA of 20% will receive 0.08 points, which is equivalent to about 1 month of waiting time.
  - Candidates with cPRA of 75% to 79% will receive 1.58 points (equivalent to 1.5 years of waiting time).
  - Candidates with cPRA of 80% to 84% will receive 2.46 points (equivalent to 2.5 years of waiting time).
  - Candidates with cPRA of 98%, 99%, or 100% will receive 24.4, 50.09, and 202.10 points, respectively.
  - The cPRA-based allocating points improve access for highly sensitized candidates. In the current UNOS allocation system,

very highly sensitized kidney transplant candidates (cPRA 99%-100%) are eligible for national sharing of donor offers.

Pediatric candidate

Prior living donor

Patient/donor HLA-A, HLA-B, and HLA-DR mismatch at the time of allocation

Prioritization of zero HLA-A, HLA-B, HLA-DR mismatch, also known as zero-mismatch (discussed in **Chapter 8: Transplant Immunobiology**)

Estimated posttransplant survival (EPTS) score

- The EPTS score is designed to ensure that those kidneys expected to function the longest are transplanted into those candidates expected to live the longest. It is based on four factors: the candidate's age, length of time on dialysis, prior transplant of any solid organ, and current diabetes status. A lower EPTS score is associated with longer posttransplant longevity.
- Candidates with EPTS scores of 20% or less will receive increased priority for offers of kidneys with KDPI scores of 20% or less. Such priority applies to both candidates inside and outside the 250-nautical mile allocation circle.
- The EPTS score will only be used in kidney allocation when the donor has a KDPI of 20% or less (KDPI defined earlier).
- EPTS scores will not be calculated for pediatric candidates until the age of 18 years has been reached.

Others

- The kidney allocation system also provides greater access to deceased donor kidneys for blood type B candidates who can safely accept a kidney from an A2 or A2B blood type donor.

- Prioritization of medically urgent candidate (The candidate receives priority when a kidney is available within a 250 nautical mile circle.)

IMMUNOSUPPRESSIVE AGENTS

The Three-Signal Model of the Alloimmune Response

T-cell activation requires three signals (**Figure 9.1**).

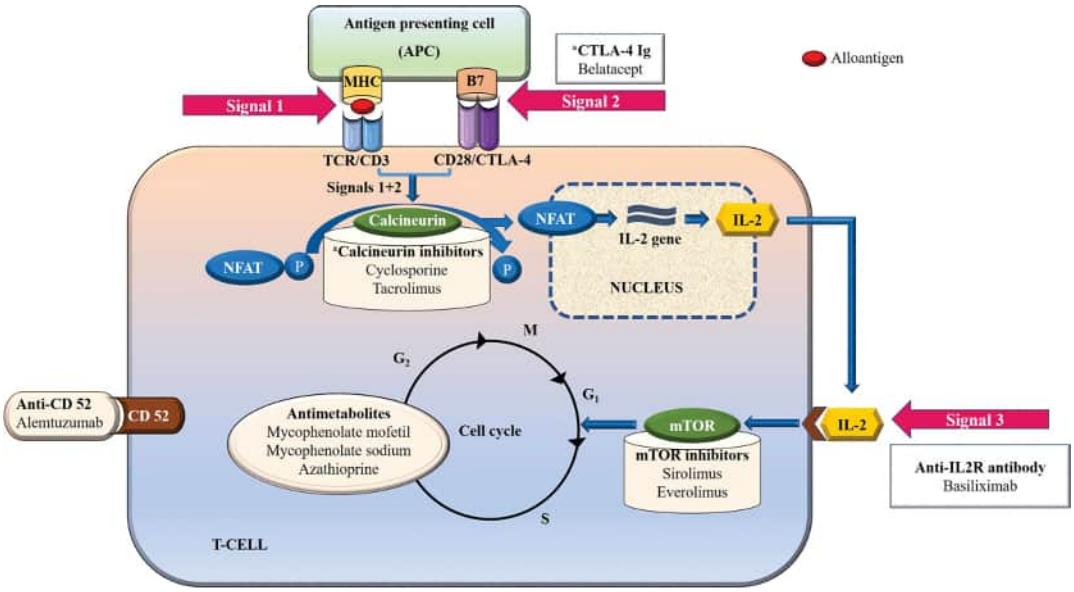

FIGURE 9.1 The three-signal model of the alloimmune response and targets of different immunosuppressive agents. Signal 1: binding of alloantigen (red oval) on the surface of the APC to TCR/CD3 complex on T cell. Signal 2: binding of B7 on the surface of APC to CD28 on T cell. These dual signals (ie, signals 1 and 2) activate the intracellular pathways that trigger T cells to activate the transcription of IL-2 and other growth-promoting cytokines. Signal 3: binding of IL-2 to its receptor leads to activation of mTOR inhibitor, which leads to T-cell proliferation.

Abbreviations: Anti-IL-2R, anti-IL-2 receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; TCR, T-cell receptor.

[a]**Calcineurin** is a phosphatase that dephosphorylates and facilitates the translocation of NFAT (and other nuclear factors) to the nucleus. Inhibition of *calcineurin* impairs the expression of IL-2 (and other growth-promoting cytokines) thereby reducing the proliferation of T cells.

Signal 1 is initiated by the binding of the alloantigen on the surface of antigen-presenting cell (APC) to the T-cell receptor (TCR)-CD3 complex.

Signal 2 is a nonantigen-specific costimulatory signal provided by the engagement of B7 on the surface of APC with CD28 on T cell. These dual signals activate the intracellular pathways that trigger T cells to activate the transcription of interleukin-2 (IL-2) and other growth-promoting cytokines. T cells also express cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a cell surface molecule that is homologous to CD28. However, unlike CD28, the binding of B7 to CTLA-4 produces an inhibitory signal that inhibits T-cell proliferation and helps terminate the immune response.

Signal 3: Engagement of IL-2 to its receptor activates the mTOR pathway to provide signal 3, which leads to cell proliferation. If a TCR is triggered without the accompanying costimulatory signal 2, the T cell is driven into an anergic state.

Antimetabolites

- Lymphocyte proliferation, which requires the synthesis of purine and pyrimidine nucleotides, is inhibited by the antimetabolites mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium, and azathioprine (AZA; discussed further in a later section).

Targets of Various Immunosuppressive Agents

The targets of various immunosuppressive agents are shown in **Figure 9.1**.

Agents targeting both signals 1 and 2

Calcineurin inhibitors (CNIs): cyclosporine and tacrolimus

- Calcineurin is a phosphatase that dephosphorylates and facilitates the translocation of the nuclear factor of activated T cells (NFAT) and other nuclear factors to the nucleus. Once translocated into the nucleus, NFAT promotes the translation of specific genes, including that of the growth-promoting cytokine IL-2.
- Inhibition of calcineurin by CNIs impairs the expression of IL-2 (and other growth-promoting cytokines), thereby reducing the proliferation of T cells.

Agents targeting signal 2

Belatacept (Nulojix) is a humanized fusion protein, composed of CTLA-4 fused with the Fc domain of human immunoglobulin G1 (CTLA-4Ig). Belatacept binds to B7 with high affinity and inhibits the costimulatory pathway.

Agents targeting signal 3

Basiliximab is a humanized monoclonal antibody that targets the α chain of the IL-2 receptor (also known as anti-IL-2 receptor or anti-CD25 antibody), blocking IL-2 mediated responses.

mTOR inhibitors: sirolimus and everolimus

The mTOR is a key regulatory kinase in the cell division process. Its inhibition reduces cytokine-dependent cellular proliferation at the G1 to S phase of the cell division cycle.

Antimetabolites

Mycophenolic acid (MPA) derivatives (Mycophenolate mofetil, mycophenolate sodium)

- Mycophenolate mofetil (Cellcept) is a prodrug that must be hydrolyzed to the active agent—MPA—in the gastric acidic milieu. MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (a rate-limiting enzyme in the novo synthesis of purines). Depletion of guanosine nucleotides by MPA has a relatively selective antiproliferative effect on lymphocytes due to their reliance on the de novo pathway of nucleotide synthesis.
- Mycophenolate sodium (Myfortic) is an enteric-coated formulation of MPA that dissolves at pH greater than 5.5. Therefore, unlike mycophenolate mofetil (MMF), mycophenolate sodium bypasses the acidic milieu of the stomach and is absorbed in the intestines.
- The use of antacids or proton pump inhibitors (PPIs) can reduce the dissolution of MMF by increasing pH. In contrast, the bioavailability of mycophenolate sodium is not affected by antacids or PPIs.

Azathioprine (AZA)

- AZA is a precursor of 6-mercaptopurine.

- AZA inhibits DNA replication and subsequent T-cell proliferation. MMF/mycophenolate sodium has largely replaced AZA due to its greater efficacy in reducing acute rejection.

Lymphocyte-depleting agents

- Antithymocyte globulin (ATG; Thymoglobulin, rabbit ATG) is a polyclonal antibody preparation made by immunization of rabbits with human lymphoid tissue. The purified immunosuppressive product contains cytotoxic antibodies directed against a variety of T-cell markers.
- Alemtuzumab is a humanized monoclonal antibody targeting CD52 on the surface of both B and T lymphocytes leading to a rapid and profound depletion of peripheral and central lymphoid cells.

Glucocorticoid

- Key component of all immunosuppressive regimens
- Modulates inflammatory mediators
- Blocks interleukin-1 (IL-1) and IL-2 production, thereby suppressing the early phase of the immune response

Basic Principles of an Immunosuppressive Protocol

A standard immunosuppressive protocol consists of *induction* and *maintenance* immunosuppression (**Table 9.8**).

Table 9.8 Components of a standard immunosuppressive protocol (immunosuppressive and nonimmunosuppressive agents)

Immunosuppressive agents	Options
Induction	• Lymphocyte-depleting agent: rabbit-derived antithymocyte globulin, aka ATG (Thymoglobulin) • Nonlymphocyte-depleting agent: basiliximab (Simulect)
Standard triple-maintenance immunosuppression • Calcineurin inhibitor (CNI)	• CNI: cyclosporine or tacrolimus • Most commonly used adjunctive agent: mycophenolic acid (MPA) derivatives

Immunosuppressive agents	Options
• Adjunctive agent • Corticosteroid	• Adjunctive agent used for special conditions (instead of MPA)[a]: azathioprine, sirolimus, or everolimus • Chronic maintenance dose of prednisone: typically 5 mg daily
Supplementary agents	Nondihydropyridine calcium channel blockers (to boost CNI drug levels)
Infection prophylaxis	• *Pneumocystis jirovecii* (trimethoprim-sulfamethoxazole, atovaquone, dapsone) • Cytomegalovirus (acyclovir, valganciclovir). Other: letermovir (see text) • Antifungals (nystatin, fluconazole)

[a]See text.

Induction therapy

- Induction is used to rapidly create a therapeutic net state of immunosuppression in the first few days or weeks after transplantation to prevent rejection.
- Induction therapy can be classified into lymphocyte-depleting and nonlymphocyte-depleting agents.

Lymphocyte-depleting agents: ATG (Thymoglobulin, rabbit ATG), alemtuzumab (anti-CD52 on T-lymphocyte)
Nonlymphocyte-depleting agent: basiliximab (anti-IL-2-receptor antibody)

- The choice of one induction agent over the other is generally based on individual immunologic risk factors, anticipated delayed graft function (DGF), or both (**Table 9.9**).

Table 9.9 Induction therapy: lymphocyte-depleting versus nonlymphocyte-depleting agents

Lymphocyte-depleting agents[a]	Nonlymphocyte-depleting agents	Comments
Rabbit-derived antithymocyte globulin aka ATG or Thymoglobulin	Basiliximab	ATG induction commonly used in: • High immunologic risk patients (highly sensitized or re-allograft transplant recipient). Examples: presence of pretransplant DSA and/or high cPRA[b] • Anticipated DGF to avoid early exposure to cyclosporine or tacrolimus (nephrotoxic). DGF has also been suggested to heighten the risk of acute rejection (see text). Basiliximab induction commonly used in: • Low to moderate immunologic risk transplant recipients (cPRA cutoff values for ATG vs basiliximab induction vary among centers and clinicians. However, most clinicians use basiliximab induction if cPRA <20%-30% and no DSA.)
Alemtuzumab		Alemtuzumab is used at a small number of transplant centers in the United States.

Abbreviations: cPRA, calculated panel reactive antibody; DGF, delayed graft function; DSA, donor-specific antibody.

[a]Lymphocyte-depleting agents can cause first-dose reaction or cytokine release syndrome including chills, fever, arthralgia, and rarely serum sickness.

[b]DSA and calculated panel reactive antibody (cPRA) are discussed in **Chapter 8: Transplant Immunobiology.**

- In the presence of anticipated DGF due to donor acute tubular injury (aka acute tubular necrosis or ATN), it is important to maintain adequate immunosuppression. It has been suggested that endothelial injury upregulates and exposes donor histocompatibility antigens, adhesion molecules, and costimulatory molecules, heightening the risk of acute rejection. Induction therapy with lymphocyte-depleting agent and delayed introduction of CNI may avoid the additive injury associated with CNI nephrotoxicity (due to afferent arteriolar vasoconstriction) while reducing the risk of allograft rejection at the time of heightened immunogenicity.

Maintenance immunosuppression

Maintenance immunosuppression is used to sustain a therapeutic net state of immunosuppression to prevent rejection. A standard immunosuppressive regimen consists of triple-drug therapy: CNI (cyclosporine or tacrolimus) + adjunctive agent + corticosteroid.

Calcineurin inhibitor: The choice of tacrolimus over cyclosporine A (CSA) or vice versa can be made based on the potential adverse effects of these agents. The side effect profiles of cyclosporine and tacrolimus are shown in **Table 9.10**. Over the past two decades, there has been a steady trend in the United States and Europe toward greater use of tacrolimus.

Table 9.10 Side effect profiles of cyclosporine and tacrolimus

Cyclosporine A (CSA)	Tacrolimus (Tac)	Comments
Nephrotoxicity	Nephrotoxicity	
Hypertension and sodium retention	Hypertension and sodium retention	CSA > Tac
Hyperlipidemia	Hyperlipidemia	CSA > Tac
Diabetes mellitus	Diabetes mellitus	Tac > CSA
Neurotoxicity (headache, tremors, confusion, paresthesia)	Neurotoxicity (headache, tremors, confusion, paresthesia, insomnia)	Tac > CSA
Thrombotic microangiopathy	Thrombotic microangiopathy	
GI (diarrhea, abdominal pain, nausea, vomiting. Elevated liver enzymes and mild hyperbilirubinemia[a])	GI (diarrhea, abdominal pain, nausea, vomiting. Elevated liver enzymes and mild hyperbilirubinemia[a])	[a]Reversible with dose reduction or drug discontinuation
Hyperkalemia	Hyperkalemia	
Hypomagnesemia	Hypomagnesemia	
Hyperchloremic metabolic acidosis	Hyperchloremic metabolic acidosis	

Cyclosporine A (CSA)	Tacrolimus (Tac)	Comments
Hyperuricemia, gout	Hyperuricemia, gout	CSA > Tac
Others: Hirsutism, gingival hyperplasia	*Others:* Alopecia, pancreatitis	

Adjunctive agents: MMF, mycophenolate sodium, sirolimus, everolimus, AZA

- MMF or mycophenolate sodium is the most commonly used adjunctive agent. The side effect profiles of MMF and mycophenolate sodium are shown in **Table 9.11**.

Table 9.11 Side effect profiles of mycophenolate mofetil and mycophenolate sodium

Mycophenolate mofetil (Cellcept)	Mycophenolate sodium (Myfortic) (enteric-coated mycophenolic acid derivative formulation)
Diarrhea, nausea, vomiting, abdominal pain, flatulence, dyspepsia	Potentially less gastrointestinal toxicity compared with mycophenolate mofetil
Hematologic effects: leukopenia, leukocytosis (less commonly seen than leukopenia), anemia, thrombocytopenia	Hematologic effects: leukopenia, leukocytosis (less commonly seen than leukopenia), anemia, thrombocytopenia
Comments: More than 2 g/d is usually not well tolerated.	Comments: Myfortic 180 mg = Cellcept 250 mg (similar efficacy)

- AZA, sirolimus, or everolimus is generally used in place of MMF for special indications (discussed in the following text).
  - Azathioprine
    - AZA use is safe in pregnancy.
    - May be used in place of MPA derivatives in patients who are intolerant to MPA (generally due to gastrointestinal [GI] side effects)
    - Avoid use with allopurinol or febuxostat (xanthine oxidase inhibitors) because of the inhibition of AZA metabolism by xanthine oxidase inhibitors.
  - Sirolimus or everolimus (mTOR inhibitors)

- Potential beneficial effect in patients with history of malignancy, particularly skin cancers, renal cell carcinoma (RCC), or Kaposi sarcoma. Its use in posttransplantation lymphoproliferative disorder (PTLD) has inconsistently been shown to be beneficial.
- Not recommended in the early postoperative period (may impair wound healing and delayed recovery of acute tubular injury)
- The side effect profiles of sirolimus and everolimus are shown in **Table 9.12**.

NOTE

MMF (or mycophenolate sodium) and sirolimus (or everolimus) must be discontinued in anticipation of pregnancy. MPA derivative use in pregnancy has been shown to be associated with first-trimester pregnancy loss and congenital malformation, whereas mTOR inhibitor use in pregnancy has been reported to be associated with fetal mortality, decreased fetal weight, and delayed ossification of skeletal structure. AZA is safe for use in pregnancy.

FYI

All kidney transplant recipients also receive prophylactic therapy with antibiotic, antiviral, and antifungal agents. Nondihydropyridine calcium channel blocker (CCB) is commonly used to boost CNI or mTOR inhibitor levels (see **Table 9.8**). The use of diltiazem or verapamil may permit CNI dose reductions up to 40% and 30% to 50%, respectively.

Table 9.12 Side effect profiles of mammalian target of rapamycin inhibitors (sirolimus or everolimus)

Potential side effects	Comments
• Delayed recovery of acute tubular injury (acute tubular necrosis) • Impaired wound healing • Increased risk of lymphocele formation • May potentiate calcineurin inhibitor nephrotoxicity • Oral ulcers • Diabetogenic	• Not recommended in the early postoperative period • Not recommended in patients with preexisting proteinuria ≥500 mg/d or at the discretion of the clinician (Practice may differ among centers.) • Calcineurin inhibitor target level should be lowered when used in combination with

Potential side effects	Comments
• Proteinuria (Nephrotic syndrome and FSGS associated with sirolimus use have been reported.) • Dyslipidemia (hypercholesterolemia; may cause significant hypertriglyceridemia) • Peripheral edema • Pulmonary toxicity • Thrombotic microangiopathy • *Others*: acne, rash, anemia, thrombocytopenia, decreased testosterone	mammalian target of rapamycin (mTOR) inhibitors.

Abbreviation: FSGS, focal and segmental glomerulosclerosis.

Steroid-free or CNI-free maintenance immunosuppressive protocol

Steroid withdrawal (CNI + MPA derivatives dual therapy)

- Must be individualized based on immunologic risk
- Use of a lymphocyte-depleting agent for induction therapy is recommended.
- Safe in low-immunologic risk patients at short-term follow-up
- The 2016 Cochrane review suggests that steroid avoidance and withdrawal after kidney transplantation significantly increase the risk of acute rejection. There is no difference in patient mortality or graft loss up to 5 years after transplantation.
- Long-term consequences of steroid avoidance and withdrawal remain unclear due to the lack of prospective long-term studies.

Belatacept in CNI-free protocol

- Clinicians must be familiar with its use.
- De novo belatacept: may be used as an alternative to CNI therapy in selected low-immunologic kidney transplant recipients. Discussion is beyond the scope of this chapter.
- CNI to belatacept conversion therapy: may be considered in low-immunologic risk patients with biopsy-documented CNI toxicity or

CNI-induced thrombotic microangiopathy (TMA) and absence of acute rejection

- Belatacept use has been shown to improve kidney function and metabolic outcomes including HTN, diabetes, and hyperlipidemia through CNI avoidance. Despite an increase in early rejection, belatacept use has been suggested to decrease long-term death and allograft loss.
- Typically used in combination with basiliximab induction, MPA derivatives, and corticosteroids: belatacept + MPA derivatives + corticosteroid
- Adverse effects: edema, leukopenia, diarrhea, constipation, HTN, cough, nausea, vomiting, headache, hypo- or hyperkalemia, among others
- Increased risk of cytomegalovirus (CMV) disease and severe CMV and BK viremia (DNAemia) has been observed. In CMV high-risk kidney transplant recipients (D+/R−), increased risk of CMV primary infection and a prolonged course of viral replication has been reported.

NOTE

U.S. Food and Drug Administration (FDA) black box warning: Belatacept is contraindicated in Epstein-Barr virus (EBV)-naïve kidney transplant recipients or in those with unknown EBV serostatus due to increased risk of PTLD predominantly involving the central nervous system.

Drug-Drug Interaction

Important drug-drug and drug-food interactions are shown in **Table 9.13**.

Table 9.13 Drug-drug and drug-food interactions

Drugs that increase CNI levels by inhibition of CYP3A4 or by competition for its pathways	
Calcium channel blockers: diltiazem, verapamil > nicardipine	• Changing the dose of these drugs is equivalent to changing CNI dosage.

	• Changing formulation of these drugs may also affect CNI levels.
The "azole" antifungals: fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole	• The "azoles" markedly increase CNI levels. Great care must be taken when starting and stopping these drugs. • The absorption of ketoconazole and itraconazole requires acidic gastric contents. Proton pump inhibitors/H_2 blockers may reduce CNI absorption.
Macrolide antibiotics: erythromycin > clarithromycin, josamycin, ponsinomycin	Azithromycin (conflicting reports): A short course can generally be given without the need for CNI level monitoring.
Antiretroviral agents: protease inhibitors (eg, ritonavir, ritonavir/lopinavir combination therapy aka Kaletra, darunavir, indinavir, saquinavir, atazanavir, amprenavir)	• Currently, integrase inhibitor-based regimen (eg, dolutegravir or bictegravir) is preferred over protease inhibitor because it does not have interaction with CNI. • Immunosuppressive management in patients with HIV requires close collaboration with infectious disease specialists due to multiple drug-drug interactions.
Hepatitis C protease inhibitors: telaprevir/boceprevir (no longer available in the United States)	For anti-HCV direct-acting antiviral (DAA) agents and CNI-drug-drug interactions, readers are referred to www.hcvguidelines.org
Drugs against COVID-19: nirmatrelvir-ritonavir combination (Paxlovid), remdesivir	• Ritonavir is a potent CYP3A4 inhibitor that can significantly increase CNI and mTOR inhibitor levels. Paxlovid contains ritonavir, hence its use in patients receiving CNI and mTOR inhibitors should be AVOIDED. • Remdesivir use has been reported to result in significantly elevated tacrolimus levels (case series and unpublished personal observations).
Others (less well established): amiodarone, carvedilol, allopurinol, bromocriptine, chloroquine	

Drugs that decrease CNI levels by induction of CYP3A4 activity	
Antituberculous drugs: rifampin > rifabutin	• Rifampin markedly reduces CNI levels, and its use should be avoided if possible. • Pyrazinamide and ethambutol may reduce drug levels. Must monitor CNI level. • Isoniazid (INH) can be used with careful drug-level monitoring.
Anticonvulsants: barbiturates > phenytoin > carbamazepine	Oxcarbazepine (Trileptal) may decrease cyclosporine levels. Gabapentin (Neurontin) and levetiracetam (Keppra) and other drugs in this category do not appear to have significant drug interactions.
Drugs that decrease CNI levels by induction of CYP3A4 activity (*continued*)	
Corticosteroids	Discontinuation of steroid therapy may increase tacrolimus level by up to 25%.
Antidepressants herbal preparation: *Hypericum perforatum* (St. John's wort)	
Others (less well established/case reports): nafcillin, IV trimethoprim, IV sulfadimidine, imipenem, cephalosporins, terbinafine, ciprofloxacin	
Drugs or food that increase the absorption of CNIs	
Grapefruit, pomegranate, star fruit (also inhibits CYP3A4); metoclopramide	The effect of grapefruit juice may vary widely among brands and is concentration, dose, and preparation dependent.
Drugs or food that decrease the absorption of CNIs: GoLYTELY, sevelamer, olestra, cholestyramine	
Nephrotoxic drugs or drugs that may potentiate CNI toxicity	
mTOR inhibitors, NSAIDs, tenofovir, amphotericin, aminoglycosides, ACE inhibitors, ARBs	• CNI target levels should be lowered when used with mTOR inhibitors. • Amphotericin and aminoglycoside-associated nephrotoxicity may occur earlier than anticipated when used with CNI therapy.

	• Tenofovir alafenamide is a prodrug of tenofovir with significantly less nephrotoxicity compared with tenofovir disoproxil fumarate.
Commonly used herbals that may have immune-stimulating effects: Ginseng, licorice, alfalfa sprouts, astragalus	
Cholesterol-lowering agents	
Cyclosporine has an inhibitory effect on CYP3A4 and P-glycoprotein. The concomitant use of cyclosporine and statins can result in a severalfold increase in statin blood level and an increased risk for myopathy, rhabdomyolysis, and acute kidney injury.	• All statins should be started at low doses. Any increase in dose requires close monitoring. Maximal dose should be avoided. • Rhabdomyolysis associated with tacrolimus and statin use is generally seen in patients on concomitant diltiazem therapy (diltiazem is a moderate CYP3A4 inhibitor). • Concomitant lovastatin (or simvastatin) and gemfibrozil therapy increase the risk of rhabdomyolysis and should be avoided.
NOTE: Tacrolimus is a substrate but not an inhibitor of the CYP3A4 enzyme system (therefore, it does not affect *statin* drug level).	

The mTOR inhibitors (sirolimus and everolimus) interact with calcium channel blockers, antifungal agents, anticonvulsants, protease inhibitors, antituberculous agents, St. John's wort, and grapefruit juice in a manner similar to the CNIs.

NB: This table provides only a general guideline. Clinicians should see drug packet inserts for full drug-drug interactions.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CNI, calcineurin inhibitors; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs.

ALLOGRAFT REJECTION: TYPES AND TREATMENT STRATEGIES

- Allograft rejection can be classified into hyperacute, acute, and chronic rejection.
- The 2022 Banff classification of renal allograft pathology is discussed in a later section. Hyperacute rejection is not classified

under Banff categories.

Hyperacute Rejection

- With the current cytotoxic crossmatch and the advent of the single-antigen bead-based Luminex assays, hyperacute rejection has become virtually nonexistent.
- Hyperacute rejection can occur immediately following vascular anastomosis or within minutes to hours after graft revascularization.
- Hyperacute rejection uniformly results in graft loss requiring allograft nephrectomy.

Pathogenesis

- Caused by preformed antidonor HLA antibodies
- Preformed antidonor HLA antibodies bind to graft endothelial antigens and activate complement leading to severe vascular injury, thrombosis, coagulative necrosis, and obliteration of the graft vasculature.

Acute Rejection

Acute rejection can be classified into acute T-cell-mediated rejection (TCMR) or acute antibody-mediated rejection (AMR). Diagnosis requires allograft biopsy.

Acute TCMR

- Generally occurs after the first posttransplantation week and most commonly within the first 3 to 6 months after transplantation
- In unsensitized patients with low levels of preformed anti-HLA antibodies, TCMR rarely occurs in the first week.
- Acute TCMR has been suggested to be a risk factor for the development of de novo donor-specific antibodies (DSAs) and subsequent AMR.

Clinical manifestations: Most patients present with asymptomatic acute rise in SCr. In the era of potent immunosuppression, fever,

malaise, oliguria, and graft tenderness are usually absent unless immunosuppression is completely discontinued.

Pathogenesis: caused by T cells reacting to donor histocompatibility antigens expressed in the tubules, interstitium, vessels, and glomeruli to various extents

Treatment of acute TCMR based on Banff classification

See **Table 9.14** for a summary of treatment of acute TCMR.

Table 9.14 T-cell mediated rejection treatment strategies

Suspicious for acute TCMR	Type 1 acute TCMR	Type 2 acute TCMR	Type 3 acute TCMR	Chronic active TCMR
Observe and follow creatinine trend vs oral or IV steroid pulse per risk (such as degree of acute kidney injury, history of medical nonadherence, and immunologic risk)	*Banff 1A:* IV steroid pulse (5 mg/kg body weight) *Banff 1B:* IV steroid pulse or ATG per risk	*Banff 2A:* ATG *Banff 2B:* ATG	ATG	There is no standardized protocol for the treatment of chronic active TCMR. Consider maximizing antimetabolite therapy if applicable.

Abbreviations: ATG, antithymocyte globulin; IV, intravenous; TCMR, T-cell-mediated rejection.

- Suspicious for rejection: Decision to treat with corticosteroid pulse is generally based on clinical history such as severity of acute kidney injury (AKI), immunologic risk, history of medical nonadherence, and/or subtherapeutic CNI levels.
- Banff grade 1A
  - High-dose intravenous corticosteroid, usually referred to as "pulse steroid" or "SoluMedrol pulse" (methylprednisolone pulse) at 5 mg/kg body weight for 3 days. Higher doses such as 500 to 1,000 mg for 3 days do not appear to be more effective. The dose of prednisone can be continued at its previous level after completion of the pulse steroid. Some centers may elect to follow various oral steroid tapering protocols.

    - ATG should be considered in TCMR refractory to corticosteroid therapy (Refractory can be arbitrarily defined as failure of SCr to improve or deterioration of graft function despite three "daily methylprednisolone pulse."). Note that there may be a delay in SCr improvement by 2 to 5 days following completion of steroid pulse. Clinical judgment is required.
- Banff grade 1B
    - Choice of high-dose intravenous corticosteroid versus ATG such as Thymoglobulin generally requires clinical correlation.
    - ATG is generally employed in patients with moderately severe to severe AKI or in those who develop acute TCMR in the early posttransplantation period. ATG should also be considered in those who fail to respond to pulse corticosteroids (particularly when there is rapid deterioration of renal function).
- Banff grade 2A or 2B

ATG (eg, Thymoglobulin)

- Banff grade 3

ATG

Acute AMR

Clinical manifestations

- Allograft dysfunction is frequently more severe than that of TCMR.
- AMR with concomitant features of TCMR may be seen.
- AMR is a risk factor for chronic rejection.

Pathogenesis

- Acute AMR is generally caused by DSA against HLA.
- Although uncommon, non-HLA DSAs have also been implicated in AMR (eg, anti-MHC class-I-related chain A [MICA] and MHC class-I-related chain B [MICB] antibodies, antiendothelial antibodies, or angiotensin receptor 1 antibodies).

Treatment of acute AMR

- Standard of care: plasmapheresis and intravenous immunoglobulin (IVIG)

    - The DSA mean fluorescence intensity threshold to initiate plasmapheresis differs among centers and clinicians.
    - Plasmapheresis in late-onset AMR (arbitrarily defined as >1 year) is of unclear benefit (data lacking).
    - Standard IVIG dose: 2 g/kg body weight total dose (usually given in two divided doses)
- C4d negative AMR should be treated using the same approach as C4d positive AMR.
- Other treatment modalities (Clinicians must be familiar with its use.):
    - Agents targeting B cells: rituximab
    - Agents targeting plasma cells (bortezomib): Limited efficacy data, seldom used. Significant adverse effects have been reported.
    - Agents targeting the complement system (eculizumab): Eculizumab has not been shown to be effective in C4d negative active and chronic active AMR. Efficacy and safety remain to be determined. Note: meningococcal vaccination recommended at least 2 weeks prior to eculizumab therapy. If vaccination is given less than 2 weeks prior to the first dose, start Penicillin V and continue it until 2 weeks after vaccination (or azithromycin 500 mg twice daily if there is a Penicillin allergy). The CDC recommends Penicillin V 500 mg bid prophylaxis for the duration of eculizumab therapy.
    - Other agents: tocilizumab (anti-IL-6 receptor antibody), clazakizumab (anti-IL-6 antibody), C1 inhibitors. Discussion is beyond the scope of this chapter.
- Treatment of acute AMR associated with non-HLA DSA (such as anti-angiotensin II type 1 [AT1] receptor antibodies, antiendothelial antibodies, and MICA discussed earlier)
    - Treatment is generally similar to that in patients with AMR and anti-HLA DSA.
    - Patients with anti-AT1 receptor antibody-associated AMR should also receive angiotensin II receptor blockers (eg, losartan). The latter may inhibit AT1-receptor antibody-mediated effects.

Table 9.15 summarizes the potential mechanisms of action of various treatment modalities for AMR.

Table 9.15 Potential mechanisms of action of various treatment modalities for AMR

Treatment modalities	Potential mechanism(s) of action and comments
Plasmapheresis	• Removes circulating alloantibodies **Comments:** may stimulate rebound immunoglobulin production
Intravenous immunoglobulin (IVIG)	• Anti-idiotypic antibodies (inhibits anti-HLA antibody) • Suppress or eliminate anti-HLA reactive T and B cells. • Induce apoptosis of B cells. • Downregulate antibody production by plasma cells. • Inhibit complement-mediated damage. • Inhibit cytokine signaling pathway and alloimmunization via blockade of T-cell receptor. • Immune modulation **Comments:** removed by plasma exchange (infuse after pheresis)
Agent targeting B cells: Rituximab	• Anti-CD20 monoclonal antibodies • May induce naïve and memory B-cell depletion • Plasma cells lack CD20 and are unaffected by rituximab. **Comments:** • Treat AMR. • Use as part of a conditioning regimen in patients with preformed anti-HLA antibodies or ABO incompatibility.
Agent targeting plasma cells: Bortezomib	• Proteasome inhibitor; induce plasma cell apoptosis • Reduce donor-specific antibody (DSA) production by plasma cells. **Comments:** • Rescue therapy for AMR refractory to IVIG/rituximab (small studies) • Limited efficacy data and significant adverse effects (seldom used)
Agents targeting the complement system: Eculizumab C1 esterase inhibitor	**Eculizumab** • Terminal complement inhibitor (binds to C5, preventing cleavage of C5 to C5a and C5b, and the formation of C5b and MAC)

Treatment modalities	Potential mechanism(s) of action and comments
(C1-INH) BIVV020	• Protects endothelium from injury caused by existing antibodies • Preventive or rescue therapy (based on small studies) • Treatment of AMR (based on case reports) • Not effective in C4d-negative active and chronic AMR (Efficacy may be limited to acute complement-mediated processes.) • RCTs evaluating its efficacy and safety are lacking. **Other agents requiring further studies: C1-INH:** inhibit multiple enzymes, including inhibition of complement activation by interruption of assembly of C1s and C1r in the classic pathway. **BIVV020:** selectively target activated serine protease C1s[a]
Anti-interleukin 6 (IL-6) receptor monoclonal antibody: Tocilizumab	• Rescue therapy for DSA-positive chronic active AMR with evidence of transplant glomerulopathy not responsive to standard therapy (IVIG + rituximab ± plasmapheresis) (case series)
Anti-IL-6: Clazakizumab	Ongoing clinical trial (at the time of this writing).[b]

Abbreviations: AMR, antibody-mediated rejection; HLA, human leukocyte antigen; MAC, membrane attack complex; RCTs, randomized controlled trials.

[a]A multicohort, randomized, phase 2, open-label study to assess the efficacy, safety, and pharmacokinetics of BIVV020 for prevention and treatment of AMR in adult kidney transplant recipients is ongoing.

[b]ClinicalTrials.gov Identifier: NCT03744910.

Manipulation of maintenance immunosuppression following treatment of acute TCMR and/or acute AMR

- Increase maintenance immunosuppressive drug target levels (tacrolimus or cyclosporine).
- In patients who are on cyclosporine-based immunosuppression, consider switching from cyclosporine to tacrolimus.
- Maximize antimetabolite therapy as tolerated (if patient is not already on maximum dose of MMF or mycophenolate sodium).

Chronic Rejection

- Graft deterioration in the late posttransplantation period can be due to alloimmune or non-alloimmune causes, or both. Diagnosis requires allograft biopsy.
- Chronic rejection is an alloimmune-dependent process associated with T-cell-mediated and/or antibody-mediated injury.
- Chronic rejection of the kidney transplant is the most common cause of graft loss in the late posttransplantation period.

Risk factors: prior acute rejection episodes (TCMR or AMR or both), poor HLA matching, prior sensitization or posttransplantation development of HLA antibodies (de novo or anamnestic response), underimmunosuppression, or medical nonadherence

Clinical manifestations: Patient generally presents with gradual deterioration in kidney allograft function with or without various degrees of proteinuria.

Pathogenesis

- Chronic AMR is a process in which donor-specific anti-HLA antibodies develop, followed by immune-mediated injury to the kidney allograft. Continuous antibody-mediated injury can lead to separation of the endothelial cells from the underlying basement membrane. These cells, will, in turn, lay down a new basement membrane matrix resulting in the so-called basement membrane duplication and the histologic appearance of transplant glomerulopathy (TG).
- Interstitial inflammation in the areas of interstitial fibrosis and tubular atrophy (i-IFTA) is considered a potential lesion of chronic active TCMR. However, the pathogenesis of i-IFTA and the extent to which it represents a manifestation of TCMR remain to be studied.

Treatment

Chronic active TCMR

The optimal management of chronic active TCMR remains to be defined. **Table 9.14** summarizes the treatment strategies for acute

TCMR and chronic active TCMR (opinion based).

Chronic active AMR

- There is currently no effective therapy for chronic active AMR. Consider maximizing antimetabolite therapy as tolerated if applicable (ie, MMF 1,000 mg twice a day or mycophenolate sodium 720 mg twice a day).
- The presence of chronic transplant glomerulopathy (CTG) portends poor graft prognosis, particularly when associated with positive C4d staining.
- Tocilizumab has been used in the treatment of DSA-positive chronic active AMR with variable success.
- Clazakizumab (anti-IL-6-antibody): Phase 3 clinical trial to evaluate the safety and efficacy of clazakizumab in the treatment of chronic active AMR is currently ongoing (NCT03744910).

KIDNEY ALLOGRAFT BIOPSY

Histopathologic Terminologies

Acute tubular injury (aka acute tubular necrosis) (Figure 9.2)

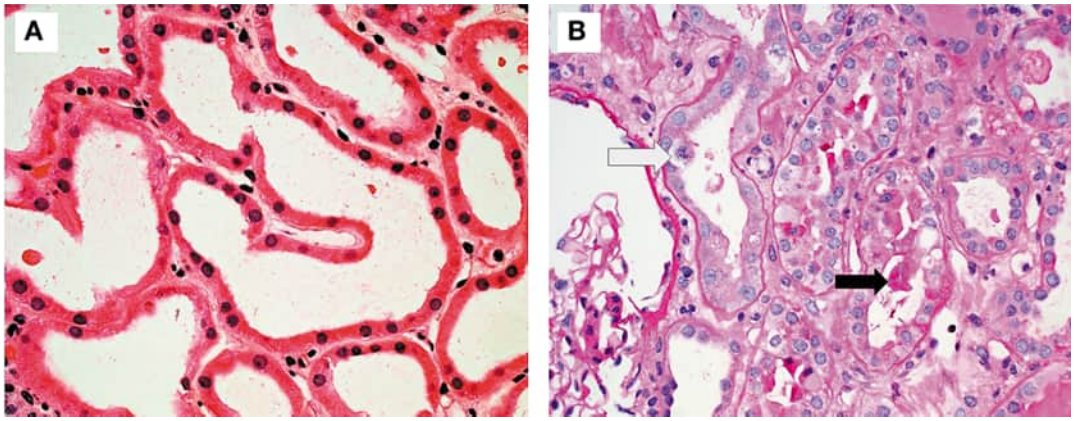

FIGURE 9.2 Acute tubular injury. A. Tubular cells are flattened and have lost brush borders (hematoxylin and eosin stain, 400×). B. Severe tubular injury with epithelial cell necrosis and sloughing into tubular lumina (black arrow). A tubular mitotic figure is present (white arrow) (periodic acid-Schiff stain, 400×).

Proximal tubule epithelial cell flattening, loss of brush border staining, cellular degeneration or necrosis, mildly dilated luminae, and/or sloughed epithelial cells

Tubulitis (Figure 9.3)

Mononuclear cells within tubular walls between epithelial cells

Interstitial inflammation (see Figure 9.3)

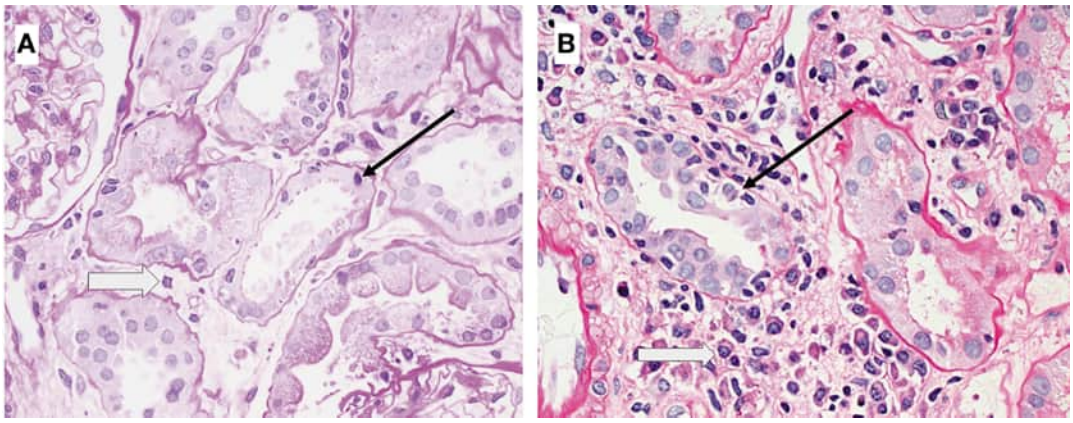

FIGURE 9.3 Interstitial inflammation and tubulitis are the histologic features of acute T-cell-mediated rejection (TCMR). A. Acute TCMR grade IA. Moderate tubulitis represented by 5 to 10 lymphocytes within a tubular cross-section (black arrow). Interstitial inflammatory cells (lymphocytes) between tubules (white arrow). B. Acute TCMR grade IB. Severe tubulitis represented by more than 10 lymphocytes within a tubular cross-section (black arrow). Dense interstitial inflammatory cells (lymphocytes and plasma cells) between tubules (white arrow) (periodic acid-Schiff stain, 400×).

Inflammatory cells between tubules in interstitial spaces and can include lymphocytes, plasma cells, macrophages, eosinophils, and/or rare neutrophils may be seen.

Intimal arteritis (aka endarteritis, endotheliitis, or v-lesions) (Figure 9.4A)

Lymphocytes underneath the endothelium in the arterial intima

Arterial transmural inflammation (transmural arteritis) and fibrinoid change (Figure 9.4B)

Inflammation extending into arterial medial layer with smooth muscle cell necrosis and fibrin deposition

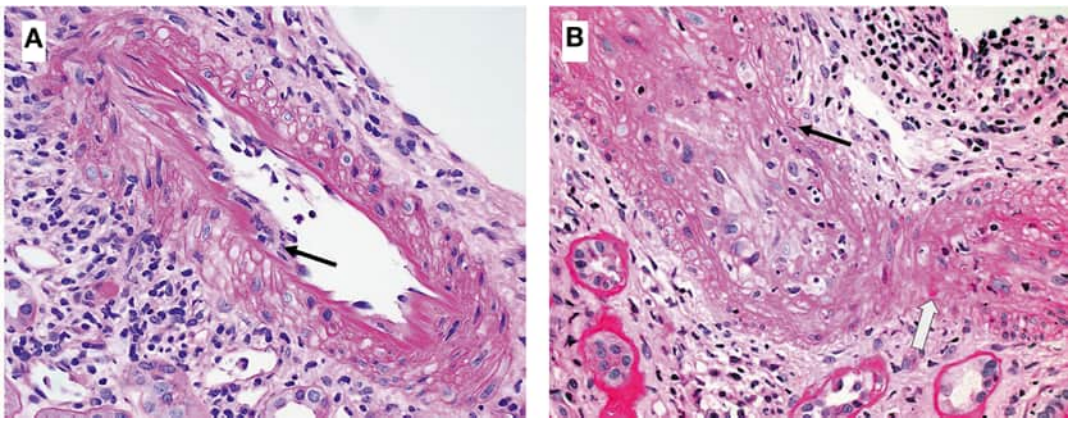

FIGURE 9.4 Vascular inflammation is a histologic feature of severe acute T-cell-mediated rejection (TCMR). These changes can also be seen with active antibody-mediated rejection. A. Acute TCMR grade IIA. Mild intimal arteritis (<25% luminal obstruction) represented by leukocytes directly beneath the artery endothelial cells within the intimal layer only (arrow). B. Acute TCMR grade III. Transmural arteritis (black arrow) with fibrinoid necrosis (white arrow) (periodic acid-Schiff stain, 400×).

Glomerulitis (Figure 9.5A)

Leukocytes and swollen endothelial cells within glomerular capillary lumens

Peritubular capillaritis (Figure 9.5B)

Leukocytes within peritubular capillary lumens

Transplant glomerulopathy (Figure 9.6)

Glomerular capillary double contours composed of subendothelial lucencies with deposition of new subendothelial basement membrane

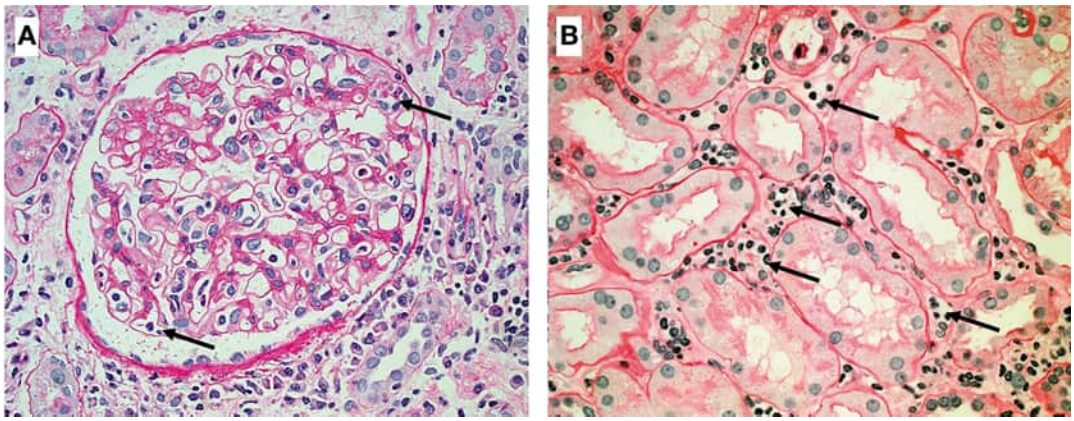

FIGURE 9.5 Microvascular inflammation is a histologic feature of active antibody-mediated rejection. A. Glomerulus affected by glomerulitis represented by increased endocapillary leukocytes and swollen endothelial cells (arrows). B. Peritubular capillaritis represented by increased peritubular capillary leukocytes (arrows) (periodic acid-Schiff stain, 400×).

Chronic transplant arteriopathy (Figure 9.7A)

Expansion of arterial intimal spaces by fibrosis admixed with mononuclear cells with or without foam cells

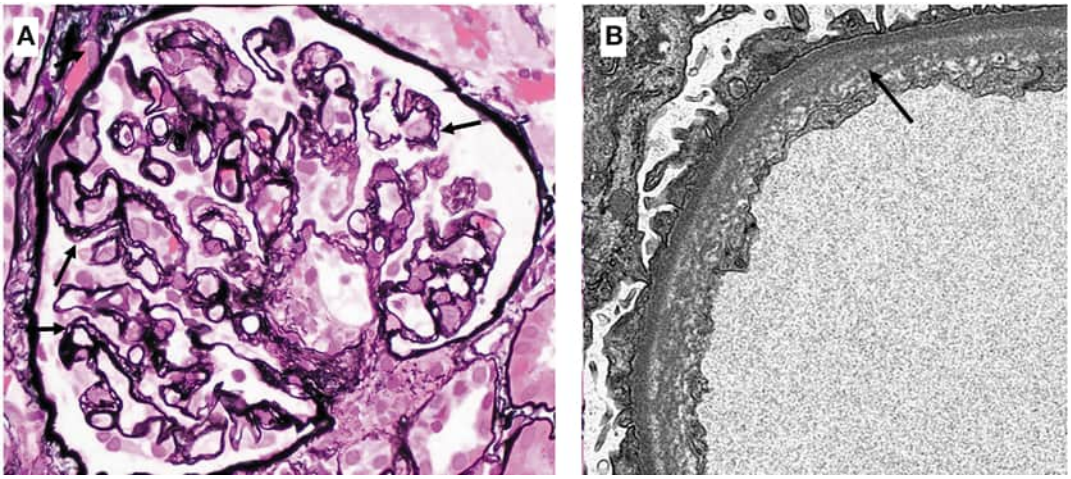

FIGURE 9.6 Transplant glomerulopathy is a feature of chronic antibody-mediated rejection. A. Glomerulus with double contours on light microscopy (arrows) (Jones Silver stain, 400×). B. Electron micrograph demonstrating multilayered capillary loop glomerular basement membrane duplication (6,300×) (arrow).

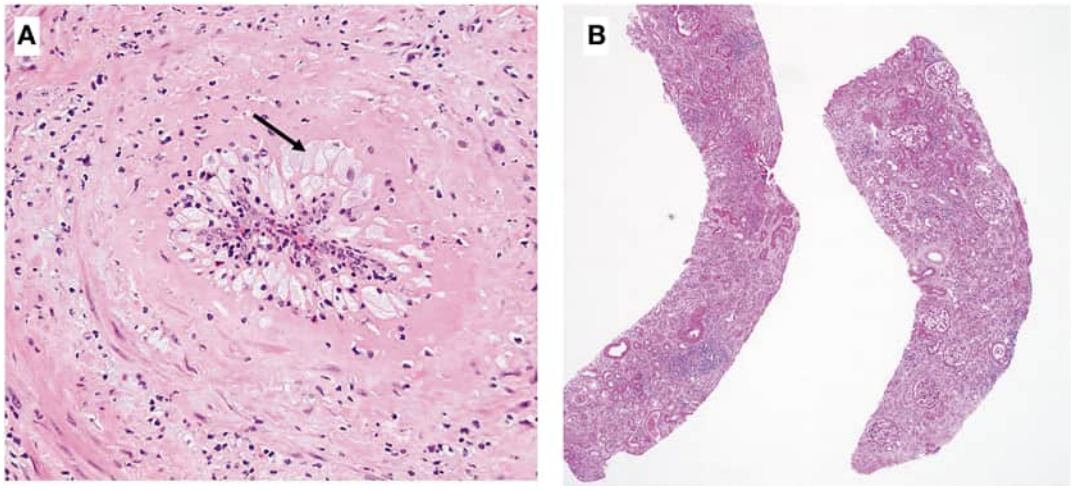

FIGURE 9.7 Chronic active T-cell-mediated rejection (TCMR). A. Chronic allograft arteriopathy (chronic active TCMR II). Arterial intimal fibrosis admixed with lymphocytes and foam cells (arrow) (H&E stain, 400×). B. Inflammation and tubulitis in areas of cortical scar can be features of chronic active TCMR (periodic acid-Schiff stain, 400×).

Thrombotic microangiopathy (Figure 9.8)

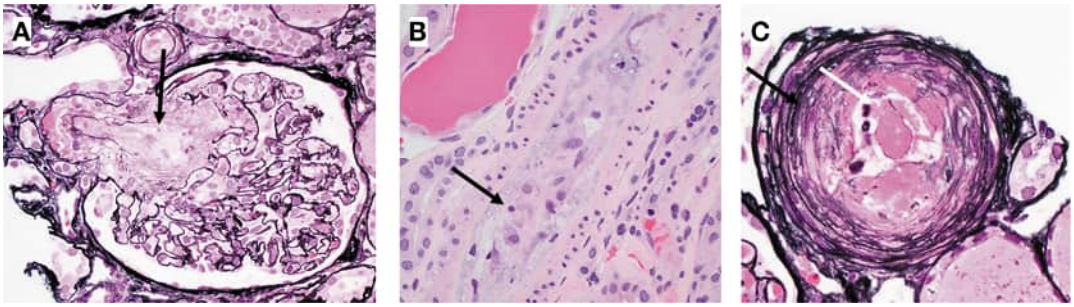

FIGURE 9.8 Thrombotic microangiopathy (TMA) can be associated with antibody-mediated rejection, calcineurin inhibitor therapy, and wide variety of conditions including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, autoimmune disorders, viral infections, and other drug toxicities. Distinguishing specific etiology on biopsy is not possible. A. Glomerular thrombosis (arrow) with early capillary loop double contours (Jones Silver stain, 400×). B. Artery with mucoid intimal edema (arrow) (hematoxylin and eosin stain, 400×). C. Arterial luminal thrombus (white arrow) with early "onion skin change" (black arrow) (Jones Silver stain, 400×).

- Luminal aggregates of platelets and/or fibrin within arterial or glomerular capillary lumens and/or subendothelial edema (mucoid intimal edema) within arteries/arterioles

- Chronic TMA can mimic TG and shows "onion skin" changes in arteries/arterioles.

C4d staining (Figure 9.9)

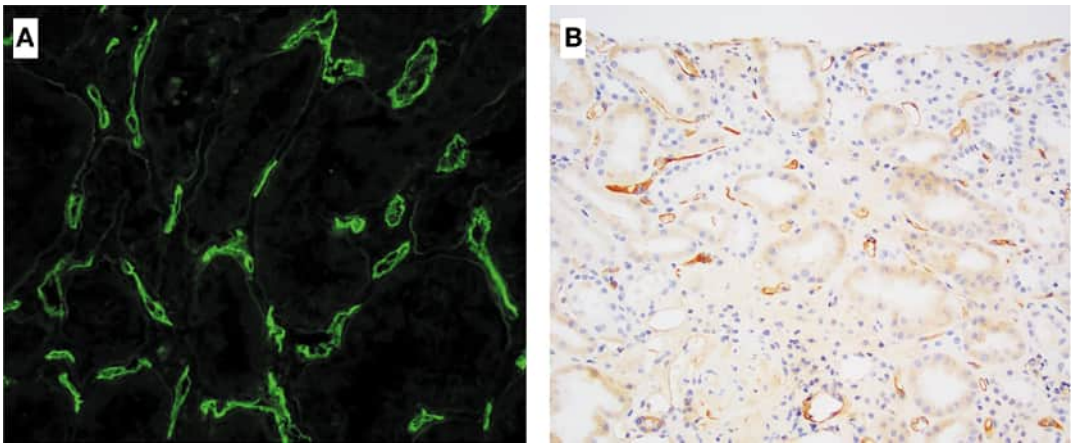

FIGURE 9.9 C4d staining of peritubular capillaries is a marker of antibody-mediated rejection. A. Immunofluorescence staining for C4d is more sensitive. B. Immunohistochemical staining for C4d is more specific (images at 400×).

- Component of the classical complement cascade that is covalently linked to tissue
- Surrogate marker of antibody endothelial cell interaction
- Staining is evaluated in peritubular capillaries and vasa recta.
- Glomerular staining is not specific and is not scored.

Proximal tubule isometric vacuolization (Figure 9.10A)

Focal proximal tubule cells with uniform cytoplasmic vacuolization often with small shrunken (pyknotic) nuclei, usually S3 segment of proximal tubule

Nodular medial hyalinosis (Figure 9.10B)

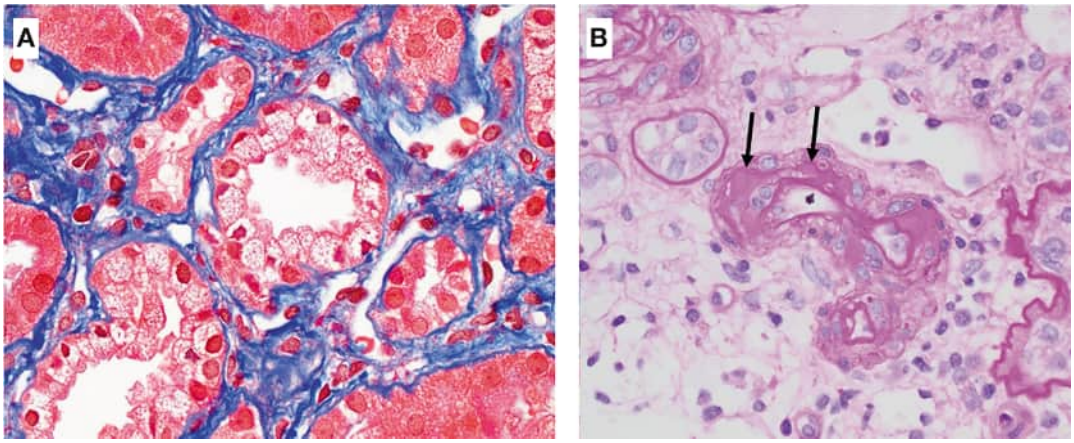

FIGURE 9.10 Acute and chronic sequelae of calcineurin inhibitors. A. Isometric vacuolization of proximal tubule cells is frequently associated with acute calcineurin inhibitor toxicity (Trichrome stain, 400×). B. Nodular medial hyalinosis (arrows) is associated with chronic calcineurin inhibitor effect.

- Nodular hyaline accumulation within the walls of arterioles
- Presumed to result from the degeneration of arteriolar smooth muscle cells

Arteriosclerosis (Figure 9.11A)

Intimal fibrosis of arteries without inflammation

Arteriolosclerosis (Figure 9.11B)

Hypertrophy of medial layer of arterioles with or without intimal hyalinization

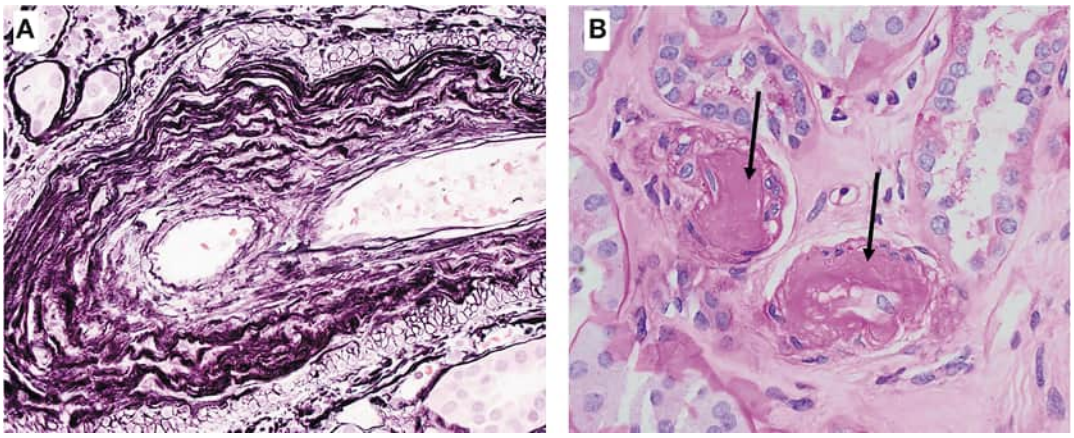

FIGURE 9.11 Chronic noninflammatory vascular changes usually related to age or chronic hypertension. A. Arteriosclerosis—expansion of the arterial intima by

fibrosis with concentric duplication of the internal elastic lamina. B. Arteriolosclerosis—subintimal accumulation of hyaline insudate beneath arteriolar endothelial cells (arrows).

Banff Classification

- Most widely accepted classification system for allograft biopsy diagnostic changes, specifically for alloimmune-related graft injury—rejection
- A working classification that is updated every 2 years
- The Banff classification is categorized into six broad categories based on presence or absence of the histopathologic features described earlier. The phenotypes/subcategories of Banff 2022 category 2 are shown in **Figure 9.12**.

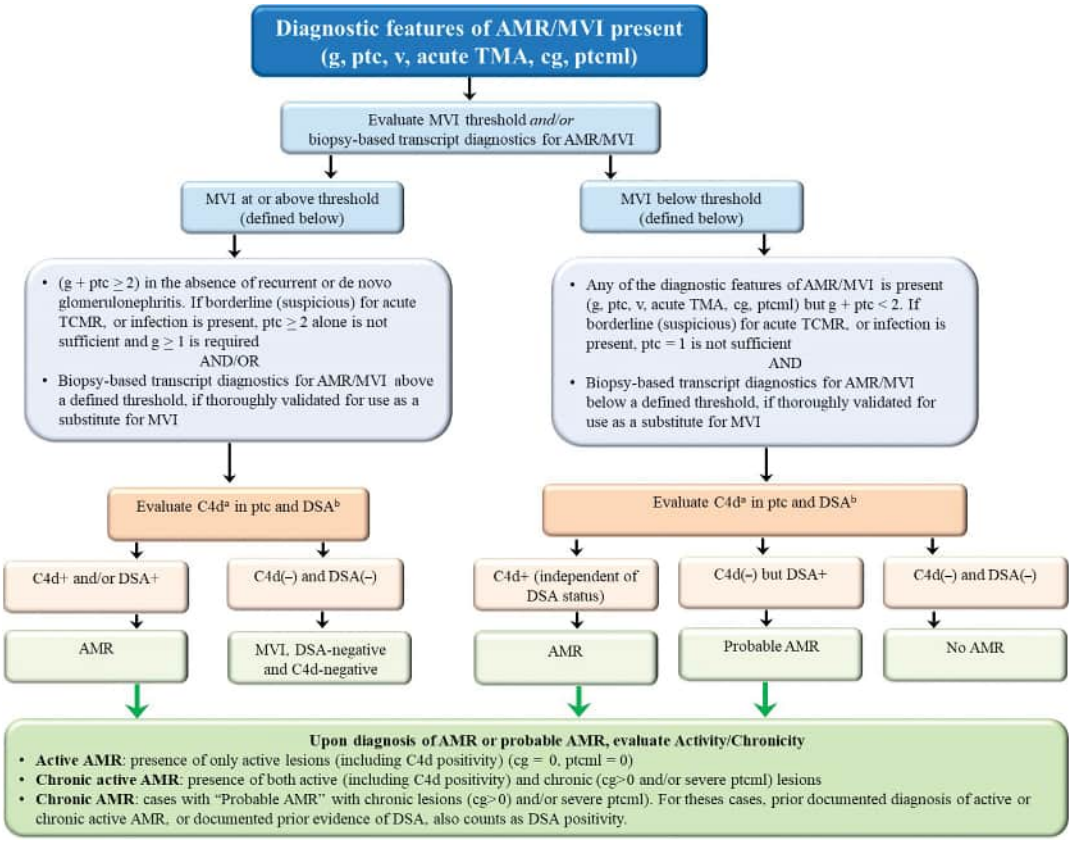
Diagnostic features of AMR/MVI present (g, ptc, v, acute TMA, cg, ptcml)
Evaluate MVI threshold and/or biopsy-based transcript diagnostics for AMR/MVI
MVI at or above threshold (defined below)
MVI below threshold (defined below)
• (g + ptc ≥ 2) in the absence of recurrent or de novo glomerulonephritis. If borderline (suspicious) for acute TCMR, or infection is present, ptc ≥ 2 alone is not sufficient and g ≥ 1 is required
AND/OR
• Biopsy-based transcript diagnostics for AMR/MVI above a defined threshold, if thoroughly validated for use as a substitute for MVI
• Any of the diagnostic features of AMR/MVI is present (g, ptc, v, acute TMA, cg, ptcml) but g + ptc < 2. If borderline (suspicious) for acute TCMR, or infection is present, ptc = 1 is not sufficient
AND
• Biopsy-based transcript diagnostics for AMR/MVI below a defined threshold, if thoroughly validated for use as a substitute for MVI
Evaluate C4d[a] in ptc and DSA[b]
Evaluate C4d[a] in ptc and DSA[b]
C4d+ and/or DSA+
C4d(–) and DSA(–)
C4d+ (independent of DSA status)
C4d(–) but DSA+
C4d(–) and DSA(–)
AMR
MVI, DSA-negative and C4d-negative
AMR
Probable AMR
No AMR
Upon diagnosis of AMR or probable AMR, evaluate Activity/Chronicity
• Active AMR: presence of only active lesions (including C4d positivity) (cg = 0, ptcml = 0)
• Chronic active AMR: presence of both active (including C4d positivity) and chronic (cg>0 and/or severe ptcml) lesions
• Chronic AMR: cases with "Probable AMR" with chronic lesions (cg>0) and/or severe ptcml). For theses cases, prior documented diagnosis of active or chronic active AMR, or documented prior evidence of DSA, also counts as DSA positivity.

FIGURE 9.12 Phenotypes/subcategories of Banff 2022 category: AMR/MVI. Abbreviations: AMR, antibody-mediated rejection; cg, chronic glomerulopathy; DSA, donor-specific antibody; g, glomerulitis; MVI, microvascular inflammation/injury; ptc, peritubular capillaritis; ptcml, peritubular capillary basement membrane multilayering; TCMR, T-cell-mediated rejection; TMA, thrombotic microangiopathy; v (aka intimal arteritis, endarteritis, or endotheliitis).

[a]C4d deposition should be evaluated in peritubular capillaries and vasa recta (C4d positive ¼ C4d2 or C4d3 by IF on frozen sections, C4d greater than 0 by immunohistochemistry on paraffin sections)

[b]Thorough testing for DSA (anti-HLA or other specificity) should be done, following the STAR guidelines (discussion is beyond the scope of this chapter). Detection of non-HLA antibodies (including ABO-incompatible transplantation) can be used as serologic Banff criterion for diagnosis of AMR, if testing protocols are sufficiently standardized and clinically validated for the appropriate clinical context.

Banff categories 1 to 5

Banff categories 1 to 5 predominantly refer to categories of transplant rejection (summarized in **Tables 9.16**, **9.17**, and **Figure 9.12**). The histopathologic features of Banff categories 2 and 4 are shown in **Figures 9.3 to 9.9**.

Table 9.16 Banff categories 1 to 5

Category 1	Category 2	Category 3	Category 4	Category 5
Normal biopsy or nonspecific changes	Antibody-mediated changes	Suspicious or borderline changes for acute TCMR	T-cell mediated rejection (TCMR)	Interstitial fibrosis and tubular atrophy (IFTA)
	See **Table 9.17**	• Up to 25% interstitial inflammation with any degree of tubulitis • >25% interstitial inflammation and up to one to four lymphocytes per tubular cross-section	**Acute TCMR** Banff 1A • >25% unscarred interstitial inflammation • Tubulitis with 5-10 lymphocytes Banff 1B • >25% unscarred interstitial inflammation • Tubulitis with >10 lymphocytes or any degree of tubulitis with tubular rupture Banff 2A	Grade I: • ≤25% cortical • IFTA (mild IFTA) Grade II: • 26%-50% cortical • IFTA (moderate IFTA) Grade III: • >50% cortical • IFTA (severe IFTA)

Category 1	Category 2	Category 3	Category 4	Category 5
			• Subendothelial artery inflammation[a] with <25% vascular luminal occlusion • Any degree of interstitial or tubular inflammation Banff 2B • Subendothelial artery inflammation[a] with ≥25% vascular luminal occlusion • Any degree of interstitial or tubular inflammation Banff 3 • Mononuclear arterial inflammation which is transmural and/or with smooth muscle fibrinoid necrosis • Any degree of interstitial or tubular inflammation • May reflect ABMR **Chronic active TCMR** Banff 1A • >25% IFTA with inflammation (i-IFTA) without other known cause of inflamed fibrosis[b]	

Category 1	Category 2	Category 3	Category 4	Category 5
			• >25% inflamed total cortical interstitial area • Tubulitis with 5-10 lymphocytes in preserved to moderately atrophic tubules Banff 1B • Changes similar to Banff 1A but tubulitis with >10 lymphocytes in preserved to moderately atrophic tubules Banff 2 • Artery with mononuclear inflammation in intimal fibrosis (chronic allograft arteriopathy)	

Abbreviation: ABMR, antibody-mediated rejection.

[a]Endarteritis, intimal arteritis, endotheliatis.

[b]Such as chronic pyelonephritis or chronic BK virus infection.

Adapted from Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T-cell- and antibody-mediated rejection. *Am J Transplant*. 2020;20(9):2318-2331.

Table 9.17 Banff category 2 (antibody-mediated changes)

Antibody-mediated rejection (AMR) and microvascular inflammation/injury (MVI)
Active AMR See **Figure 9.12** **Chronic active AMR** See **Figure 9.12** **Chronic AMR** See **Figure 9.12** **Probable AMR**

Antibody-mediated rejection (AMR) and microvascular inflammation/injury (MVI)

See **Figure 9.12**

C4d staining without evidence of rejection (must meet all the following four criteria)

1. C4d positive
2. No diagnostic features of active or chronic active AMR
3. No diagnostic features of acute or chronic active TCMR, or borderline changes
4. Biopsy-based transcript diagnostics for AMR/MVI below threshold

MVI, DSA negative, and C4d negative (must meet all the following three criteria)

1. At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥2 alone is not sufficient and g must be ≥1.
2. C4d negative
3. DSA negative

C4d staining with acute tubular injury (must meet all the following three criteria)

Acute tubular injury present
C4d positive
No diagnostic features of active or chronic active AMR
Clinical scenarios:
Early posttransplant in crossmatch positive DSA-sensitized patient → "Probable AMR"
ABO incompatibility → Likely "accommodation"
DSA negative in conventional transplants → "No AMR"

Abbreviations: DSA, donor-specific antibody; g, glomerulitis; ptc, peritubular capillaritis; TCMR, T-cell-mediated rejection.

Adapted from Naesens M, Roufosse C, Haas M, et al. The Banff 2022 Kidney Meeting Report: reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. *Am J Transplant*. 2024;24(3):338-349.

- T-cell mediated rejection:
  - Acute TCMR: Banff grades 1A, 1B, 2A, 2B, 3 (see **Figures 9.3 and 9.4**)
  - Chronic active TCMR: Banff grades 1A, 1B, 2 (see **Figure 9.7**)
- Antibody-mediated changes and microvascular inflammation:
  - Acute AMR (see **Figure 9.5**)
  - Chronic active AMR, chronic AMR (see **Figures 9.6 and 9.9**)

Banff category 6

Histopathologic changes not considered to be caused by acute or chronic rejection

- Acute tubular injury (aka acute tubular necrosis) (see **Figure 9.2**)
- Polyomavirus nephropathy, usually BK polyomavirus (BKPyV; rarely JC [John Cunningham] virus) (**Figure 9.13**):

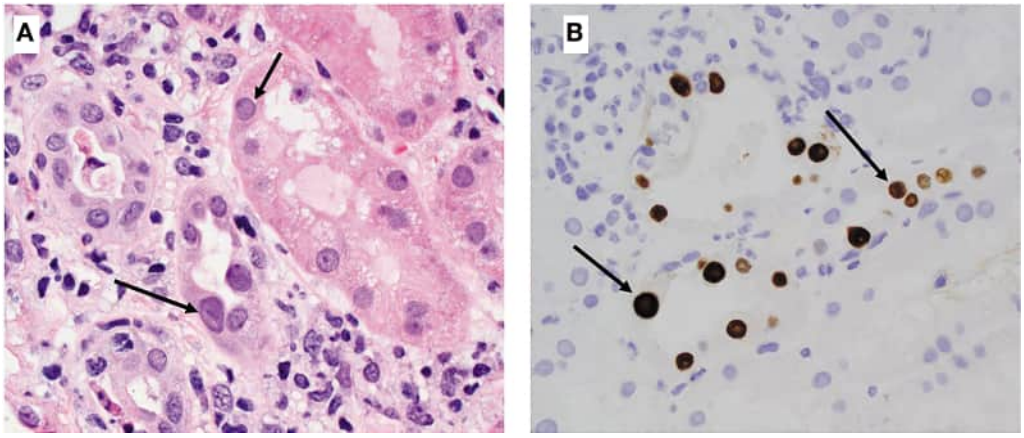

FIGURE 9.13 Polyoma (BK) virus nephropathy. A. Tubular epithelial cells with viral inclusions (arrows) (H&E, 400×). B. SV40 immunostain demonstrates strong nuclear staining (arrows) and is confirmatory of polyomavirus infection (400×).

  - Most common infection identified on allograft biopsy
  - Ascending infection from infected urothelial cells of the bladder
  - Tubulointerstitial inflammation often with prominent plasma cells; confirmed with SV40 immunostain and/or presence of viral inclusion
  - Histologic changes may be identical to acute TCMR.
- CNI nephrotoxicity (see **Figure 9.10**)
- Pyelonephritis (**Figure 9.14**)

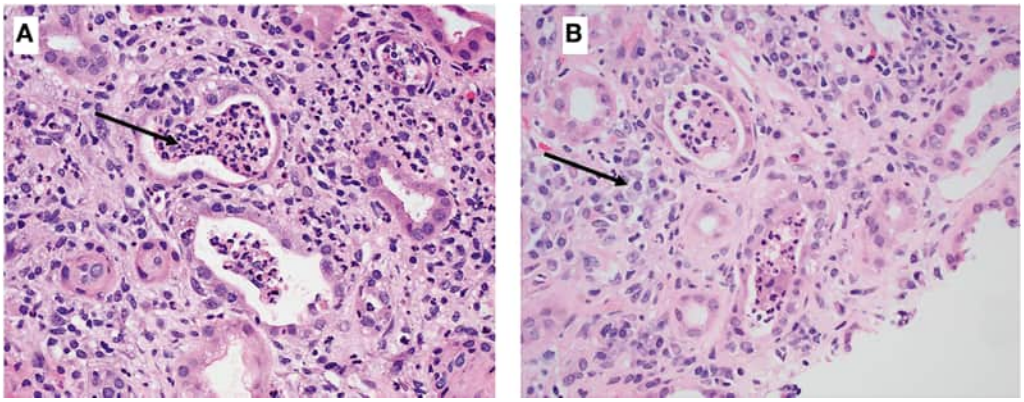

FIGURE 9.14 Pyelonephritis results from ascending bacterial infections. A. Neutrophilic intraluminal tubular cast (arrow) and adjacent neutrophilic interstitial inflammation are features of acute pyelonephritis. B. Chronic pyelonephritis typically shows increased plasma cells (arrow) and interstitial fibrosis.

- Drug-induced interstitial nephritis
- PTLDs (**Figure 9.15**)

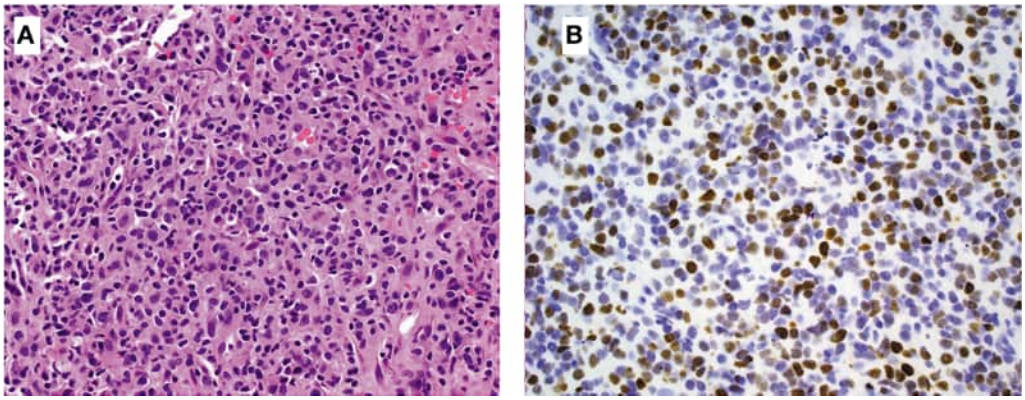

FIGURE 9.15 Posttransplant lymphoproliferative disorder (PTLD). A. Diffuse large B-cell lymphoma (H&E, 400×). B. Epstein-Barr virus (EBV) is present in the majority of cases of PTLD. (EBV-encoded small RNAs in situ hybridization, 400×.)

- Recurrent disease (**Figure 9.16**): Diseases that commonly recur include complement 3 glomerulopathy (C3G), idiopathic/primary FSGS, immunoglobulin A (IgA) nephropathy, and membranous nephropathy (MN).

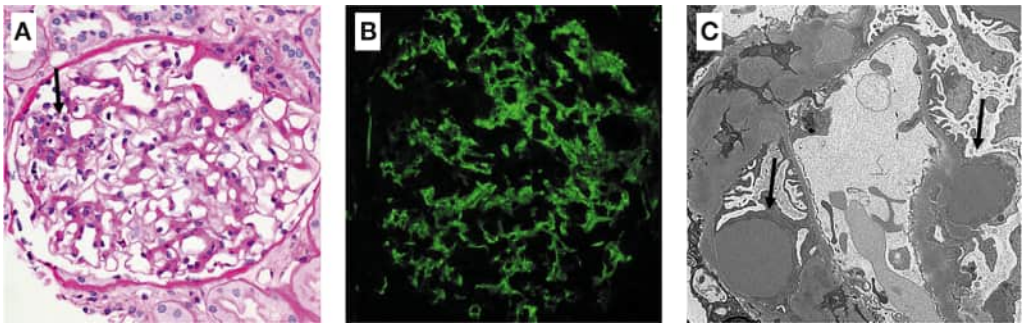

FIGURE 9.16 C3 glomerulonephritis nearly always recurs in the kidney allograft with a generally indolent course. A. Acute proliferative glomerulonephritis represented by segmental endocapillary neutrophils (arrow). B. Bright C3 immunofluorescence staining (400×). C. Subepithelial "hump-like" deposits (arrows) present on electron microscopy (4,000×).

- De novo glomerular disease (**Figure 9.17**)

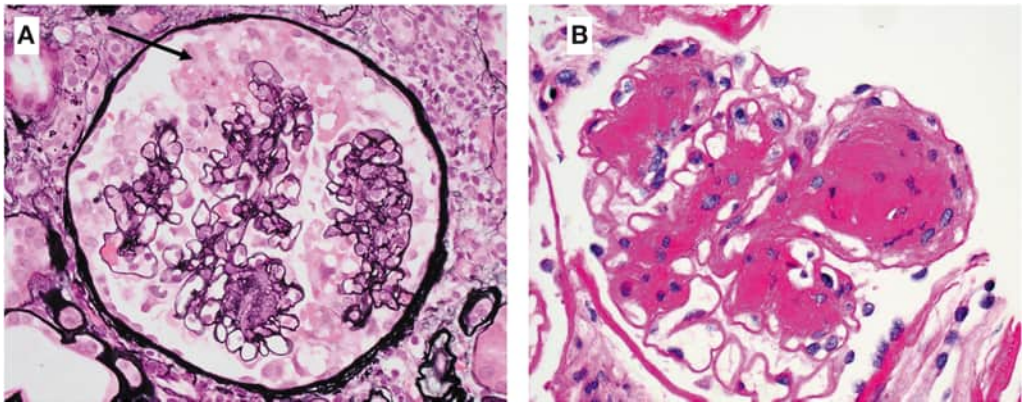

FIGURE 9.17 Examples of de novo glomerular disease in the renal allograft. A. Collapsing glomerulopathy (collapsing variant segmental glomerulosclerosis) represented by marked podocyte hypertrophy (arrow) and collapse of the underlying capillary loops (Jones Stain, 400×). B. Nodular diabetic nephropathy can develop de novo in a transplanted kidney (periodic acid-Schiff stain, 400×).

- Cytomegalovirus nephropathy (**Figure 9.18**)

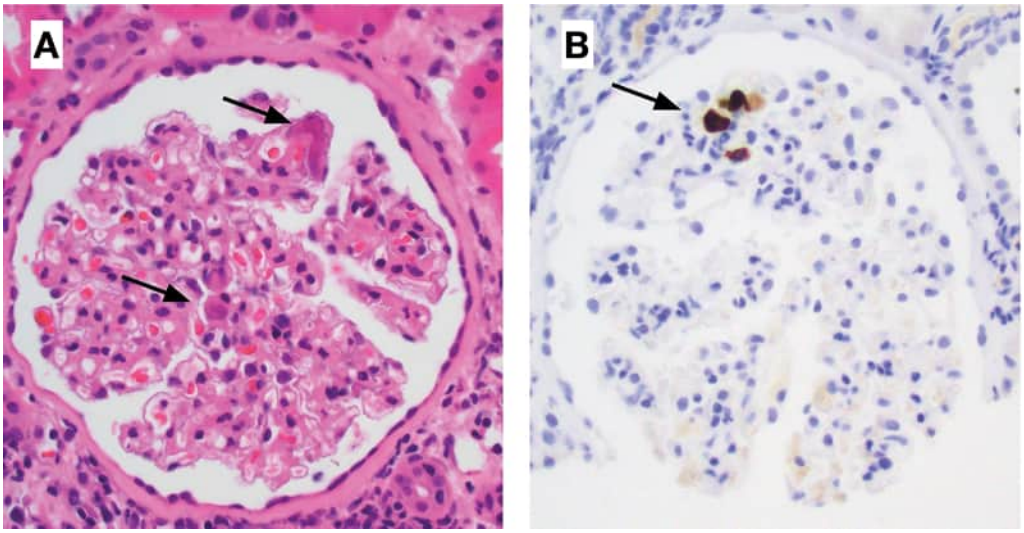

FIGURE 9.18 Cytomegalovirus (CMV) nephropathy. A. Glomerular endothelial cells with viral inclusions (arrow) (hematoxylin and eosin stain, 400×). B. CMV immunostain demonstrates strong nuclear staining (arrow) and is confirmatory of CMV infection (400×).

  - Rare infectious complication
  - Tubulointerstitial inflammation often with prominent plasma cells; nuclear and/or cytoplasmic inclusions in tubular epithelium; endothelial cells and to a lesser extent in monocyte/macrophages; immunohistochemistry needed for confirmation
- Chronic vascular changes attributable to age, HTN, or chronic vascular injury (nonrejection) (see **Figure 9.11**)
  - Arteriosclerosis/arteriolosclerosis; may be donor derived
  - Intimal fibrosis of arteries without inflammation
  - Hyalinization of arterioles other than an outer nodular pattern; similar changes can be seen in patients with diabetes.

Other Transplant Histopathology (Not Classified Under Banff Categories)

Hyperacute rejection (Figure 9.19)

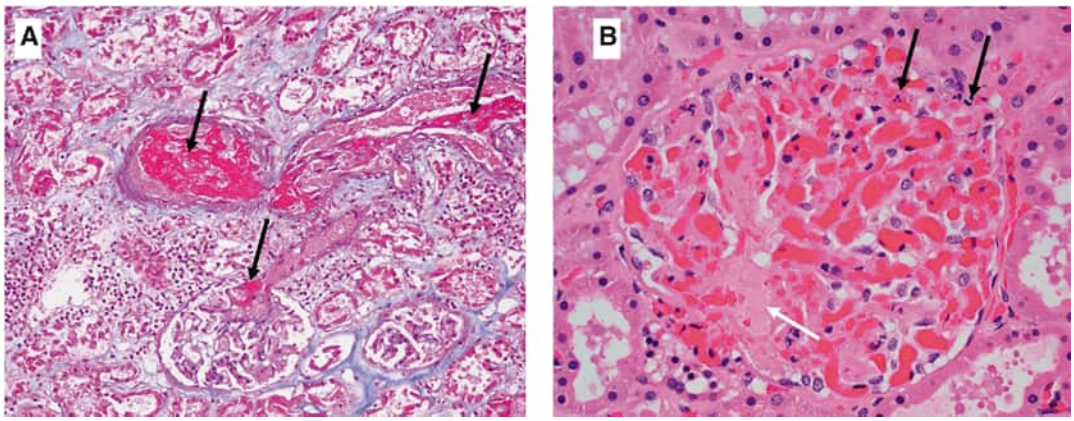

FIGURE 9.19 Hyperacute rejection is unusual in the modern transplant era. A. Hyperacute rejection with diffuse large thrombi filling arterial and arteriolar lumens (arrows) with adjacent cortical necrosis (Trichrome stain, 200×). B. Marked glomerular vascular congestion with associated small luminal thrombus (white arrow) and neutrophilic endocapillary inflammation (black arrows) (hematoxylin and eosin stain, 400×).

- Caused by preformed antidonor HLA antibodies
- Occurs immediately following or within minutes to hours of vascular anastomosis
- Exceedingly rare in the modern transplant era
- Histopathology: thrombosed arteries, arterioles, and glomerular capillaries, often with neutrophils incorporated into the thrombi; ischemic acute tubular injury; minimal interstitial or tubular inflammation

NONINVASIVE BIOMARKERS FOR EARLY DETECTION OF GRAFT INJURY AND REJECTION

Donor-Derived Cell-Free DNA

Donor-derived plasma cell-free DNA (dd-cfDNA) has emerged as a promising novel tool for noninvasive monitoring of early graft injury and rejection in kidney transplant recipients.

Method

dd-cfDNA measures DNA fragments derived from necrotic or apoptotic donor graft cells. During allograft injury from various causes, such as during an acute rejection process, a significantly higher amount of dd-

cfDNA is released, thus increasing the total percentage of the dd-cfDNA fragments relative to the total amount of cell-free DNA in recipient's plasma (dd-cfDNA/recipient's total amount of cell-free DNA expressed in percentage [%]).

Interpretation and clinical utility of dd-cfDNA

- dd-cfDNA accounts for less than 0.5% of total plasma cell-free DNA in kidney transplant recipients without allograft injury.
- In most studies, dd-cfDNA greater than 1% was found to be associated with an increased probability of detecting active rejection on biopsy (particularly AMR), whereas dd-cfDNA less than 1% was associated with absence of active rejection.
- A rising trend in serial dd-cfDNA has also been suggested to be associated with a higher likelihood of detecting active rejection.
- The combined use of dd-cfDNA and DSAs increases the pre-biopsy probability of detecting AMR.
- The Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) study demonstrated that dd-cfDNA levels less than 1% have a positive predictive value of 61% and a negative predictive value of 85% for active allograft rejection. Whereas the high negative predictive value of dd-cfDNA suggests that dd-cfDNA can be used to avoid unnecessary biopsies, performing biopsies in the setting of elevated dd-cfDNA levels may allow early diagnosis of rejection prior to the clinical rise in SCr.

Limitations of dd-cfDNA

- Levels of dd-cfDNA cannot be used to distinguish between TCMR and AMR.
- dd-cfDNA may be elevated on nonrejection pathologies associated with tissue injury such as BK polyomavirus-associated nephropathy (BKPyV-nephropathy) or CNI toxicity.
- dd-cfDNA within normal range does not exclude early TCMR.

POSTTRANSPLANTATION INFECTIOUS COMPLICATIONS AND VACCINATIONS

Vaccinations

General considerations

- All kidney transplant candidates should receive vaccinations for hepatitis B, pneumococcus, and other standard vaccinations appropriate for age and presence of ESKD.
- Household members, close contacts, and health care workers should also be fully immunized.
- Vaccinations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients.
- Live vaccines are contraindicated posttransplantation.
- Seasonal influenza vaccine (injectable) is safe and effective.
- Ensuring adequate response to hepatitis B vaccination is important to prevent transmission of donor-derived infection (from organ or blood donors).

Timing of vaccinations

- Vaccinations should be administered for 4 weeks or more before transplant to achieve optimal response and to minimize the possibility of live vaccine-derived infection in the posttransplant period.
- Vaccinations during the first 3 months after transplantation may result in suboptimal response and protection because of heavy immunosuppression. Most centers restart vaccinations 6 to 12 months after transplantation, 3 months posttransplantation for influenza during outbreaks.

Recommended vaccinations before and after transplantation are shown in **Table 9.18**.

Table 9.18 Recommended vaccinations before and after transplant

Vaccine	Vaccine type	Before transplant	≥3 mo after transplant
Mumps, measles, rubella (MMR)	Live attenuated	Yes	Contraindicated
	The presence of measles antibodies can help determine the need for vaccination or revaccination prior to transplantation.		
Diphtheria-tetanus-pertussis	Inactivated	Yes	Yes
	Diphtheria and tetanus: booster every 10 y		
Herpes zoster (Shingrix)	Inactivated	Yes	Yes
	Indicated for ≥19 y of age (recommended by ACIP)		
Poliovirus	Inactivated	Yes	Yes
	For travelers to endemic areas (eg, some parts of Asia, Africa)		
H. influenza type b	Inactivated	Yes	Yes
	Indicated for sickle cell disease, complement deficiency, or splenectomy		
Influenza A and B[a]	Inactivated	Yes	Yes
	Annually.[b] Administer to all patients who are >3 mo posttransplant. May be administered in the immediate posttransplant period during outbreaks		
Hepatitis A	Inactivated	Yes	Yes
	• Recommended posttransplant if not administered pretransplant (obtain total hepatitis A antibody. If negative, vaccination recommended) • For travelers to endemic areas		
Hepatitis B: Heplisav, Engerix	Inactivated	Yes	Yes
	Recommended posttransplant if not administered pretransplant. Monitor titers for response to vaccination. Repeat vaccination series if needed.		
Pneumococcal vaccines (recommended by ACIP for solid organ	Inactivated	Yes	Yes

Vaccine	Vaccine type	Before transplant	≥3 mo after transplant
transplant recipients and candidates ≥ 19 y of age)	• For adults who have not previously received PPSV23, administer PCV20 (or PCV21), no additional vaccination for *Pneumococcus* is required. • For adults who just received PPSV23 but have not received PCV20 (or PCV21), wait 12 mo before administering. *If PCV20 (or PCV21) is not available, PCV15 may be used in combination with PPSV23; ideally, PCV15 is followed 8 wk later by PPSV23. If PPSV23 was received first, wait 12 mo before administering PCV15*.		
Neisseria meningitides (both quadrivalent and group B vaccines)	Inactivated	Yes	Yes
	Recommended for patients with properdin terminal component deficiencies or receiving eculizumab (or ravulizumab) therapy, or those with functional or anatomic asplenia. Others: military members, travelers to high-risk areas, college freshmen living on campus		
Human papilloma-virus (HPV)	Inactivated	Yes	Yes
	Nonpregnant female candidates aged 11-26, males aged 11-21		
COVID-19	mRNA[c] or protein based[c]	Yes	Yes
	Should follow CDC guidelines for patients with weakened immune systems		
RSV[d]	Consider seasonal RSV vaccines for patients >60 y of age[e].		

Abbreviations: ACIP, American Committee on Immunization Practices; CDC, Center for Disease Control and Prevention; PCV13, pneumococcal 15-valent conjugate vaccine; PCV20, pneumococcal 20-valent conjugate vaccine; PCV21, pneumococcal 21-valent conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; RSV, respiratory syncytial virus.

[a]Live-attenuated nasal influenza vaccine has been removed from the US market.

[b]If possible, patients being treated for or recently treated for allograft rejection should avoid vaccinations until 3 months after treatment to ensure optimal immune response. However, vaccination should not be delayed if such delay represents more of a risk than the risk of impaired response. All transplant recipients over age 65 should receive the high-dose vaccine where available.

[c]Recommended by the CDC for use in the United States: mRNA (the 2023-2024 updated Pfizer-BioNTech, Moderna), protein based (the 2023-2024 updated Novavax).

[d]Available vaccines: Arexvy, mResvia, or Abrysvo.

[e]Should consider especially if >70 years of age, history of lung disease, or in the setting of lung transplantation.

Risk Factors for Posttransplant Infectious Complications

Donor-derived infections

Unrecognized infections from the donor may be transmitted to recipient.

Recipient-related risks

- Net state of immunosuppression: intensity and duration of immunosuppression
- Surgical instrumentation, wound, abdominal fluid collections
- Underlying medical risks (eg, DM, uremia)
- Increased patient age
- Hypogammaglobulinemia: Posttransplant monitoring of IgG levels and immunoglobulin replacement therapy have variably been reported to reduce infection rates in patients with hypogammaglobulinemia (especially IgG <400 mg/dL). Prospective controlled trials are lacking.
- Neutropenia and leukopenia:
  - Drug induced: thymoglobulin, MMF, AZA, sirolimus, valgancyclovir, trimethoprim-sulfamethoxazole, dapsone, or possible idiosyncratic drug-drug reaction
  - The use of granulocyte colony-stimulating factor (GCSF) is considered safe and effective in kidney transplant recipients.
- Infections with immunomodulating viruses

Environmental exposures: nosocomial, immediate living surroundings, endemic/epidemic, colonization, travel

Timetable of Posttransplant Infectious Complications

Infection follows cardiovascular disease as the second most common cause of death with a functioning graft in kidney transplant recipients. Both the type and occurrence of infections in the immunocompromised transplant recipient follow a timetable pattern (**Table 9.19**). However, the timing of infections may be altered by intensity of immune suppression, use of antimicrobial prophylaxis, and patient exposures. All transplant recipients should be counseled to minimize environmental exposure (primarily avoidance of pigeon droppings and areas of active building construction).

Table 9.19 Timetable of infections

Time period	Infectious agents
Month 1	**Bacterial (sites and sources):** surgical wound, intra-abdominal lymphoceles, hematomas, urine leak; vascular access or instrumentation[a]; anatomic or functional genitourinary tract abnormalities[b]; respiratory tract; *Clostridium difficile* or center-specific multidrug-resistant species **Viral:** uncommon except for HSV **Fungal:** *Candida* species predominate (recipient colonization or donor derived). **Comments:** Common nosocomial bacterial pathogens and *Candida* species predominate. Risk can be mitigated by appropriate prophylaxis (**Tables 9.20** and **9.21**). Minimize or avoid environmental exposure at all times after transplant (primarily avoid pigeons and areas of active building construction).
Months 1-6	**Viral** • CMV, HSV, VZV, EBV, BK polyomavirus (new infection or reactivation) • HBV and HCV may occur as de novo or reactivation of latent disease. Newer oral anti-HBV agents have decreased the incidence of HBV reactivation. Unlike HBV therapy, which is suppressive rather than curative, HCV treatment with highly effective direct-acting antiviral agents can achieve sustained viral response and can be considered curative. • Others: HHV-6, HHV-7, influenza, parainfluenza, RSV, adenovirus **Fungal:** *Aspergillus* species, *Cryptococcus*, agents of mucormycosis **Bacterial** • Recurrent urinary tract infections or pyelonephritis • *Nocardia*, *Listeria*, *Mycobacterium* species, *Legionella* **Parasitic:** *Pneumocystis jiroveci*, *Toxoplasma*, and *Strongyloides* species

Time period	Infectious agents
	Comments: unconventional or opportunistic infections due to immunosuppression; risk can be mitigated by appropriate prophylaxis (see **Tables 9.20** and **9.21**). Minimize or avoid environmental exposure.
More than 6 mo posttransplant	**Stable patients on low-dose immunosuppressants** Community-acquired respiratory and GI viral pathogens **Hx of multiple rejection episodes requiring intensified immunosuppression** Viral infections (invasive CMV such as CMV colitis or pneumonitis, VZV, parvovirus B19), late opportunistic infections (*Pneumocystis*, *Cryptococcus*, *Listeria*, nocardiosis), tuberculosis **Persistent infections:** papillomavirus, BK polyomavirus. Newer oral anti-HBV agents and HCV direct-acting antiviral agents have decreased the incidence of posttransplantation HBV reactivation and eradicated HCV infection, respectively. Treatment may halt progression of liver disease. **Regional:** Cocci- or paracoccidioidomycosis, histoplasmosis, blastomycosis **Deep-seated infections** (eg, osteomyelitis, paravertebral abscess): risks: chronic skin infections, poorly controlled diabetes, peripheral vascular disease **Associated with malignancies:** EBV (PTLD), papilloma (squamous cell carcinoma), HSV (cervical cancer), HHV-8 (Kaposi sarcoma) **Comments:** infection risks associated with duration and intensity of immunosuppression and epidemiologic and environmental exposures

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-6, human herpes virus 6; HHV-7, human herpes virus 7; HHV-8, human herpes virus 8; HSV, herpes simplex virus; Hx of, history of; PTLD, posttransplantation lymphoproliferative disorder; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

[a]Such as catheters, drains, urinary stents.

[b]Such as ureteral stricture, vesicoureteric reflux, neurogenic bladder.

Month 1 after transplantation

- Donor- and recipient-derived infections with common nosocomial bacterial microorganisms and *Candida* species predominate.
- Most bacterial infections involve wounds, catheters, and drainage sites.
- Aspiration pneumonia and urinary tract infections (UTIs) are common.

- UTI preventive measures: early urethral catheter removal and antibiotic prophylaxis
- Infections caused by multidrug-resistant bacteria are center specific.

Month 1 to 6 after transplantation

Unconventional or opportunistic infections secondary to immunosuppression are most common.

Viral infections

- Common viral infections including CMV, herpes simplex virus (HSV), varicella zoster virus, and EBV
- HBV and HCV may occur de novo or reactivation of latent disease.
  - The advent of newer oral anti-HBV agents (such as tenofovir alafenamide) results in a decrease in the incidence of reactivation of latent disease (long-term suppressive therapy required).
  - Unlike HBV therapy which is suppressive rather than curative, HCV treatment with drug regimen consisting of highly effective DAA agents results in sustained viral response in most patients, and treatment is considered curative (for antiviral therapy see **Chapter 10: Pharmacology**).
- Community-acquired respiratory viruses are a common hazard.
- Viral infections may further impair immunity and increase the risk for additional opportunistic infections.
- BK Polyoma virus (BKPyV) infection is an important cause of allograft loss (see also "BK polyomavirus" section).

Fungal infections

Repeated courses of antibiotics and corticosteroid therapy increase the risk of fungal infections.

After 6 months

Patients can be arbitrarily divided into three categories in terms of infection risks.

Category 1 (70%-80% of patients) consists of patients with satisfactory or good allograft function, on relatively low doses of immunosuppressants, and no history of chronic viral infection:

- The risk of infection is similar to that of the general population.
- Community-acquired respiratory viruses constitute the major infective agents.
- Opportunistic infections are unusual unless environmental exposure has occurred.

Category 2 (approximately 10% of patients) consists of those with chronic viral infection (eg, CMV, EBV, BKPyV, papillomavirus).

- In the setting of immunosuppression, chronic viral infections may accelerate disease progression or give rise to associated complications, for example, BKPyV-nephropathy, posttransplant lymphoproliferative disease (EBV), or squamous cell carcinoma (SCC) (papillomavirus).
- As noted earlier, the advent of newer oral anti-HBV agents and HCV DAA agents results in a decrease in the incidence of posttransplantation HBV reactivation and eradication of HCV infection, respectively (such treatment may also halt progression of liver disease).

Category 3 (approximately 10% of patients) consists of those who experience multiple rejection episodes requiring repeated exposure to potent immunosuppression. These patients are the most likely to develop chronic viral infections and superinfection with opportunistic infections.

Other considerations: New infections occurring after 6 months often reflect recent exposures (eg, *L. monocytogenes* [dietary exposure], Lyme disease [tick exposure], and malaria [travelers to endemic areas]).

Suggested antimicrobial prophylactic therapy in kidney transplant recipients is shown in **Table 9.20**.

Table 9.20 Posttransplantation antimicrobial prophylaxis

Prophylaxis	Regimen	Comments
Pneumocystis jirovecii	First line: trimethoprim-sulfamethoxazole (TMP-SMX) × 6-12 mo[a] (lifelong in some, especially thoracic organs)	• TMP-SMX also reduces the incidence of *Toxoplasma gondii*, *Listeria monocytogenes*, and *Nocardia asteroides* and reduces the incidence of UTI in kidney transplant recipients.

Prophylaxis	Regimen	Comments
	Second line (sulfa allergies)[b]: atovaquone, dapsone, or aerosolized pentamidine	• Check glucose-6-phosphate dehydrogenase prior to initiation of dapsone. • Be aware of the risk of methemoglobinemia on dapsone.
Fungal	Nystatin S&S or fluconazole[c]	• Fluconazole recommended in high-risk recipients (eg, simultaneous pancreas-kidney or simultaneous liver-kidney transplant recipients, history of coccidioidomycosis, or patients who live in endemic areas)
CMV (see **Table 9.21**)	Acyclovir, valganciclovir, ganciclovir, letermovir (FDA approved for CMV prophylaxis in D+/R−)[d]	• Acyclovir[e] for HSV and VZV prophylaxis for patients not on CMV prophylaxis

Abbreviations: CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HSV, herpes simplex virus; S&S, swish and swallow; UTI, urinary tract infection; VZV, varicella zoster virus.

[a]Restart trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis × 3 months after any SoluMedrol pulse or antibody treatment (duration of prophylactic therapy may vary among centers).

[b]Listed in order of preference. Consider adding fluoroquinolones or other agents for antibacterial activity for higher-risk recipients.

[c]The authors advocate lifelong therapy in patients with history of coccidioidomycosis or in those who live in endemic areas.

[d]Letermovir does not have HSV coverage. Letermovir-treated patients should receive HSV prophylaxis (eg, acyclovir, famciclovir, or valacyclovir).

[e]May use acyclovir, famciclovir, or valacyclovir (center dependent).

Screening and Management of Common Posttransplant Viral Infections

Cytomegalovirus

CMV infection generally refers to asymptomatic CMV seroconversion detected during CMV surveillance.

CMV infection categorization

- Primary infection: donor seropositive (D+), recipient seronegative (R−)

- Reactivation of endogenous latent virus: D+/R+ or D−/R+
- Superinfection with a new virus in a seropositive recipient: D+/R+

Clinical presentations

- Primary CMV infection is usually more severe than reactivated infection or superinfection.
- CMV disease refers to acute symptomatic CMV infection associated with various signs and symptoms including:
  - CMV syndrome: fever, fatigue, leukopenia, and/or thrombocytopenia and evidence of CMV DNAemia (formerly known as CMV viremia)
  - Invasive CMV disease involving various organ systems including the liver, GI tract, lung, or kidney allograft. Clinically, patients may present with hepatitis, esophagitis, colitis, pneumonitis, pancreatitis, or AKI.

CMV diagnosis

- Screening for CMV is best performed using PCR-based methods for CMV DNA. Whole blood may result in higher CMV DNA titers than plasma. It is best to use one specimen type for comparison.
- CMV DNA assay is highly specific and sensitive for the detection of CMV DNAemia whereas pp65 antigenemia is a semiquantitative fluorescent assay in which circulating neutrophils are stained for nonspecific uptake of CMV early antigen (pp65). With the widespread availability of nucleic acid testing (NAT), antigen-based method has largely been replaced by CMV DNA testing.
- PCR results may vary significantly among laboratories. CMV quantitative nucleic acid testing (QNAT) calibration based on the WHO International Reference Standard is recommended.
- Serum quantitative CMV assays in patients with invasive colitis and gastritis or neurologic disease including chorioretinitis are often negative. Patients suspected to have tissue-invasive CMV disease but with negative QNAT or pp65 antigenemia should have tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease.

CMV prevention can be achieved by prophylaxis or preemptive therapy.

- Prophylactic therapy involves antiviral beginning in the immediate postoperative period and continuing for a finite period (ie, 3-6 months).
- Preemptive therapy entails close CMV surveillance weekly for 12 weeks after transplant and initiation of treatment only in patients who are found to reach a certain threshold of positive CMV DNA by PCR (threshold to treat may differ among centers).
- Both approaches are recommended in the 2018 International Consensus Guidelines for at-risk kidney transplant recipients.
- Prophylactic therapy: oral valganciclovir (Suggested CMV prophylaxis protocol is shown in **Table 9.21**.)

Table 9.21 Suggested cytomegalovirus prophylaxis/preemptive protocol

2018 International Consensus Guidelines

D+/R−
- Valganciclovir 900 mg orally once a day × 6 mo OR Preemptive therapy
- After the end of prophylaxis, consider CMV DNA weekly × 3 mo.

R+ (D− or D+)
- Valganciclovir 900 mg orally once a day × 3 mo OR Preemptive therapy

D−/R−
- Acyclovir[a] 400 mg once a day (for herpes prophylaxis) × 3 mo (author's center practice)
- CMV DNA screening when clinically indicated (or if exposure to high volume of blood products)

2019 AST Infectious Diseases Community of Practice Guidelines

D+/R−
- Prophylaxis: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir × 6 mo
- Preemptive therapy (if logistic support is available): weekly CMV DNA (or pp65 antigenemia) for 12 wk after transplant. If a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg orally twice a day (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test.

R+ (D− or D+)
- Prophylaxis: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir × 3 mo
- Preemptive therapy (if logistic support is available): weekly CMV DNA (or pp65 antigenemia) for 12 wk after transplant. If a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg orally twice a day (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test.

D−/R−

2018 International Consensus Guidelines

- CMV prophylaxis not required
- HSV1- or HSV2-seropositive individuals should receive anti-HSV prophylaxis during the early period after transplantation.

Abbreviations: AST, American Society of Transplantation; CMV, cytomegalovirus; D, donor; HSV, herpes simplex virus; IV, intravenous; R, recipient.

NB: Acyclovir, valganciclovir, ganciclovir, famvir, valacyclovir: Dose adjustment for renal function necessary.

[a]May use acyclovir, famvir, valacyclovir.

Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*. 2018;102(6):900-931; Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13512.

Management of CMV

- For mild clinical symptoms: oral valganciclovir 900 mg twice daily (adjusted for GFR)
- For severe disease, high viral load, significant GI disease, or life-threatening disease or in those intolerant to oral medication, intravenous ganciclovir 5 mg/kg every 12 hours, adjusted for GFR should be used (2018 International Consensus guidelines).
- Treatment duration (2018 International Consensus Guidelines):
  - Therapy should be continued until clearance of CMV DNAemia (with the use of highly sensitive QNAT, therapy may be discontinued if CMV DNA is less than the lower limit of quantification. Confirmatory testing should be done 1 week after discontinuing therapy).
  - Generally, CMV disease should be monitored once weekly using CMV QNAT (or pp65 antigenemia) to assess virologic response.
- Patients with CMV disease should remain on full therapeutic dose of antiviral therapy until CMV DNA load (or antigenemia) is undetectable (or very low, with ultrasensitive diagnostics). After completion of full-dose treatment, consider continuing weekly monitoring for CMV DNA for 8 to 12 weeks, primarily in those at higher risk for relapse.

Other considerations in the management of CMV disease

- Cautious reduction of immunosuppression should be considered in moderate to severe disease, in slow or nonresponders, and in those with high viral load or leukopenia.
- Monitor graft function closely during CMV disease. Late-onset CMV disease occurring more than 2 years after transplant has been shown to be associated with poor transplant outcomes.
- The beneficial effect of adding IVIG or CMV Ig to existing antiviral therapy is unclear but may be considered for patients with life-threatening disease, CMV pneumonitis, resistant virus, or other severe forms of disease.
- When ganciclovir-resistant strain is suspected, obtain genotypic resistance testing (most common mutations: UL97 or UL54 gene mutation). Consider high-dose ganciclovir, maribavir, or foscarnet (potential for nephrotoxicity and synergistic nephrotoxic effect with CNIs). Maribavir is an oral agent that inhibits UL97 phosphotransferase and stops viral maturation and egress. It should NOT be coadministered with ganciclovir or valganciclovir. Monitor CNI and mTOR inhibitor drug levels closely due to drug-drug interaction with maribavir (may increase drug levels).
- Measuring anti-CMV cell-mediated immunity (using QuantiFERON-CMV or T-SPOT. CMV assays to measure the level of T-cell IFN-γ production after CMV antigen exposure) to assess the risk of CMV infection or disease and to guide therapeutic duration/management is a subject of ongoing clinical research.

FYI

Letermovir is a viral terminase inhibitor that was recently approved by the FDA for use in CMV prophylaxis in high-risk CMV seronegative recipients of a CMV seropositive donor kidney (D+/R−). However, it does not have HSV coverage. Letermovir-treated patients should receive HSV prophylaxis (eg, acyclovir, famciclovir, or valacyclovir). Advantages of letermovir over valganciclovir: lack of myelotoxicity and renal dose adjustment not required for eGFR of greater than 10 mL/min.

BK polyomavirus

- BK polyomavirus (BKPyV) is a ubiquitous human polyomavirus with a seroprevalence rate of greater than 80% to 90% among the adult

population worldwide.

- After primary infection, BKPyV preferentially establishes latency within the genitourinary tract and frequently reactivates in the setting of immunosuppression.

BK-associated clinical syndromes:

- Asymptomatic BKPyV-DNAuria (formerly known as BK viruria) with or without BKPyV-DNAemia (formerly known as BK viremia)
- BKPyV-nephropathy
- Less commonly seen: interstitial nephritis, and ureteral stenosis and obstruction
- BKPyV-DNAuria generally precedes BK-DNAemia by a median of 4 weeks; BKPyV-DNAemia commonly precedes BKPyV-nephropathy by a median of 8 weeks.
- BKPyV-DNAemia is seen in 10% to 20%, and biopsy-proven BKPyV-nephropathy in 8% (range 1%-15%) of patients in the first 12 months after kidney transplantation. Subsequently, BKPyV-DNAemia and BKPyV-nephropathy are seen in another 10% to 20% for the next 24 months, and in another 1% to 10% for the next 3 to 5 years.

BKPyV-nephropathy

- BKPyV-nephropathy is an important cause of allograft dysfunction and graft loss.
- BKPyV-nephropathy most commonly presents with an asymptomatic rise in SCr between 2 and 24 months after transplantation (median 9 months).
- Urinalysis is usually unremarkable but may reveal pyuria, hematuria, and/or cellular casts consisting of renal tubular cells and inflammatory cells.
- A definitive diagnosis of BKPyV-nephropathy requires allograft biopsy.
- Histopathologic findings of BKPyV-nephropathy (see **Figure 9.13**)
  - BKPyV viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium

- Interstitial mononuclear inflammation, often with many plasma cells, degenerative changes in tubules, and focal tubulitis (may mimic acute rejection)
- BKPyV infection and acute rejection may occur simultaneously. Distinguishing between BKPyV-nephropathy and acute rejection or the presence of both can be a diagnostic challenge. Interested readers are referred to Kotton CN, Kamar N, Wojciechowski D, et al. The second international consensus guidelines on the management of BK polyomavirus in kidney transplantation. *Transplantation*. 2024;108(9):1834-1866. doi:10.1097/TP.0000000000004976

Posttransplant BK virus screening

- 2009 KDIGO Clinical Practice Guidelines
  - Plasma QNAT screening should be performed at any of the following conditions:
    - Monthly for the first 3 to 6 months after transplant then every 3 months until the end of the first posttransplant year
    - Whenever there is an unexplained rise in SCr
    - After treatment of acute rejection
  - Reduce immunosuppression when plasma BKPyV loads are persistently greater than 10^4 copies/mL.
- 2024 Second International Consensus guidelines on the management of BKPyV in kidney transplantation
  - Plasma QNAT screening should be performed:
    - In all kidney transplant recipients monthly until month 9, and then every 3 months until 2 years posttransplant (3 years for pediatric kidney transplant recipients).
    - If allograft dysfunction
    - If allograft biopsy is performed (surveillance or indication)
  - If plasma BKPyV DNA loads are 1,000 to 10,000 copies/mL (or equivalent): perform confirmatory testing within 2 to 3 weeks. In patients with sustained plasma BKPyV DNA loads of greater than 1,000 copies/mL (or equivalent), monitor BKPyV DNA every 2 to 4 weeks to assess dynamics and response to intervention.

    - In kidney transplant recipients requiring increased immunosuppression or antirejection therapy, resume screening for the next 3 months.
    - Immunosuppression reduction is recommended for patients with:
        - Plasma BK-DNAemia between 1,000 and 10,000 copies/mL (or equivalent) on two measurements within 2 to 3 weeks. Allograft biopsy is not required for treating BKPyV DNAemic patients with baseline renal function.
        - Plasma BKPyV-DNAemia of greater than 10,000 copies/mL (based on one measurement) or if biopsy-proven BKPyV-nephropathy even if plasma BKPyV DNA load results needed to confirm the diagnosis are still pending.
        - Immunosuppression reduction strategies differ among centers and clinicians. Interested readers are referred to **Appendix A9.4**.
- Currently existing literature does not support the use of cidofovir, leflunomide, fluoroquinolones, or IVIG.
    - Proper randomized clinical trials are lacking to generally recommend treatment by switching from tacrolimus to CSA, or from mycophenolate to mTOR inhibitors.
    - Retransplantation after allograft loss due to BKPyV-nephropathy is feasible in otherwise suitable kidney transplant candidates if BKPyV-DNAemia is undetectable. Routine graft nephrectomy is not recommended.

Other comments

- BKPyV QNAT assays are not standardized across centers, and the sensitivity and specificity of the assays may vary.
- Optimal reduction of immunosuppressive therapy may allow sufficient reconstitution of BKPyV-specific T cells to control BKPyV replication, while maintaining adequate immunosuppression to prevent allograft rejection.
- Although immunosuppression reduction may improve BKPyV-DNAemia and subsequent development of BKPyV-nephropathy, it may increase the risk of de novo DSA development, underscoring

the need for routine DSA surveillance. Treatment should best be individualized based on the patient's immunologic risk.

- Reduction in immunosuppression is not universally effective, suggesting that the balance between viral replication and virus-specific immune surveillance determines the clinical course of BKPyV-associated clinical syndromes. Nonetheless, routine BKPyV screening and early intervention (ie, reduction in immunosuppression) may prevent the development of BKPyV-nephropathy.
- Future directions
  - Randomized controlled trials to evaluate the administration of BKPyV-neutralizing monoclonal antibodies to prevent or treat BKPyV-DNAemia/BKPyV-nephropathy
  - Development of BKPyV-specific T cells for adoptive transfer or antibody-based vaccines against BKPyV is a subject of ongoing research.
  - Phase 2 multicenter, randomized, double-blind, placebo-controlled clinical trial evaluating the safety, tolerability, and effectiveness of adoptively transferred multivirus-specific T cells (posoleucel) in kidney transplant recipients with BK-DNAemia showed that posoleucel was generally safe, well tolerated, and associated with a larger reduction of BK DNAemia compared with placebo. Study limitations: Short duration of follow-up. Lack of power to detect significant differences in clinical outcomes.

Herpes simplex virus 1, 2

- Results primarily from reactivation of endogenous latent virus, causing clinical infection within the first few months after transplantation (without prophylaxis)
- The routine use of acyclovir prophylaxis in the early posttransplantation period is recommended. See **Table 9.21** (also covered by valganciclovir for those on CMV prophylaxis).

Clinical manifestations: oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia

Treatment (2009 KDIGO Guidelines)

- Superficial HSV 1, 2 infections: Oral antiviral agent (eg, acyclovir, valacyclovir, or famciclovir) until all lesions are crusted.
- Systemic HSV 1, 2 infections: IV acyclovir and reduction in immunosuppression. IV acyclovir should be continued until the patient has a clinical response, and then switch to an appropriate oral antiviral agent to complete a total treatment duration of 14 to 21 days.
- In patients with frequent recurrences of HSV 1, 2 infections, prophylactic antiviral agent is recommended.

Varicella zoster (2009 KDIGO Guidelines)

Primary VZV infection (chicken pox): intravenous or oral acyclovir or valacyclovir and temporary reduction in immunosuppression. Treatment should be continued until all lesions have crusted.
Uncomplicated herpes zoster (shingles): Oral acyclovir or valacyclovir (better bioavailability), until all lesions have crusted.
Disseminated or invasive herpes zoster should be treated with IV acyclovir and temporary reduction in immunosuppression, until all lesions have crusted.
Prevention of primary varicella zoster should be instituted for varicella-susceptible patients after exposure to individuals with active varicella infection.

- If the transplant recipient is already immune to varicella/chickenpox by either history of disease, vaccination, or serology positive for varicella IgG, there is no need for concern or additional measures.
- If nonimmune, consider a course of acyclovir 400 mg po TID × 2 to 3 weeks or varicella immunoglobulin (VARIZIG). The latter can be expensive and difficult to obtain.

Adenovirus

Occurs in 4% to 5% of kidney transplant recipients
Risk factors: intensity of immunosuppression. Supporting evidence:

- Higher incidence in the first 3 months after transplantation
- Infection occurs in association with treatment of acute rejection.
- Resolution of the infection with immunosuppression reduction

Clinical manifestations

- Vary with the transplanted organ, with the allograft itself being the most frequent organ involved.
- Kidney transplant recipients frequently present with hemorrhagic cystitis, fever, dysuria, frequency, urgency, and gross hematuria.
- Hemorrhagic cystitis is frequently accompanied by graft dysfunction and kidney function generally returns to baseline after resolution of the adenovirus disease.

Treatment

- Reduction of immunosuppression is the mainstay of therapy.
- Cidofovir is used for the treatment of adenovirus disease by some centers, although its use is not supported by any prospective randomized clinical trials. In addition, routinely suggested dosing may not achieve therapeutic levels against adenovirus.

Hepatitis B

- Recipients who are hepatitis B core total antibody positive should either be monitored after transplant by periodic HBV viral load testing or given antiviral prophylaxis for at least 1-year posttransplant.
- Evidence of posttransplant HBV reactivation should be treated with entecavir or tenofovir. (HBV therapy and antiviral drug resistance are discussed in **Chapter 10: Pharmacology**.)
- The authors advocate antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation.
- Risk factors for HBV-associated liver disease progression: duration of infection, genotype C, high levels of HBV DNA, hepatitis C or hepatitis D coinfection, HIV coinfection, and immunosuppressive therapy (HBV genome contains a glucocorticoid-responsive element that augments viral replication. CNIs and the antimetabolite AZA have also been suggested to enhance HBV replication.)
- Chronic HBV infection is associated with increased risk of hepatocellular carcinoma. Biannual screening with ultrasound and serum α-fetoprotein is recommended.

Hepatitis C

- Active viral replication at the time of transplant has been shown to be associated with a higher incidence of long-term clinical liver disease and worse allograft function and survival compared with HCV-positive recipients with persistently negative viremia.
- HCV-associated liver disease is often progressive. Suggested risk factors for more rapid progression include alcohol misuse or HBV or HIV coinfection.
- Stable kidney transplant recipients with HCV viremia detected by PCR are routinely referred to hepatology for treatment.
- The advent of highly effective, pan-genotypic, DAA agents and the availability of oral combination agents targeting different stages of the HCV replicative cycle can potentially eradicate HCV infection in kidney transplant candidates and recipients. Interested readers are referred to HCV Guidance on the American Association for the Study of Liver Diseases and Infectious Diseases Society of America website for regular updates and dose adjustments in CNI-treated transplant recipients.
- Interferon-based therapy increases the risk of allograft rejection. However, with the advent of DAA, IFN-based therapy has become obsolete.

Pneumocystis jirovecii (Formerly Known as *Pneumocystis carinii*)

- *Pneumocystis jirovecii pneumonia* (PJP) commonly occurs 2 to 6 months after transplantation or following augmentation of immunosuppression.
- *P. jirovecii* outbreaks and person-to-person spread have been reported to occur more than 6 to 12 months after transplant.
- Common clinical presentation and radiographic findings: nonproductive cough, fever, arteriolar-alveolar mismatching, and diffuse interstitial infiltrate or focal airspace consolidation
- *PJP* prophylactic therapy (see **Table 9.20**)

- Prophylactic therapy should be reinstituted following intensification of immunosuppression (eg, pulse steroid or ATG to treat rejection).
- All exposed susceptible individuals should receive PJP prophylaxis.

Posttransplantation Diarrhea

Posttransplantation diarrhea is common and can be noninfectious (commonly drug related) or infectious in etiology.

Drug-related diarrhea

Mycophenolate mofetil is the most common cause of diarrhea in the early posttransplant period. Other GI side effects include nausea, vomiting, dyspepsia, anorexia, and flatulence.

- Dose reduction or transient discontinuation of the drug often ameliorates or resolves GI symptoms.
- Mycophenolate sodium (Myfortic, the enteric-coated formulation of MPA) has not been consistently shown to be better than the original formulation in ameliorating GI symptoms. Nonetheless, MMF to enteric-coated mycophenolate sodium conversion therapy can be considered in patients with GI intolerance associated with MMF use.

Sirolimus, tacrolimus, and cyclosporine have all been suggested to cause diarrhea to variable extent. Diarrhea may cause elevation in tacrolimus levels due to reduced presystemic metabolism in gut wall via P-glycoproteins and CYP 3A4/5 (see **Chapter 10: Pharmacology**).

Infectious causes of diarrhea

Most commonly encountered bacterial pathogen: *Clostridium difficile*

- Diagnostic testing: stool toxin or PCR
- Transplant-specific risk factors: ATG therapy and hypogammaglobulinemia
- Treatment:
  - First episode: oral vancomycin or fidaxomicin
  - Recurrences: fidaxomicin or prolonged, tapered, oral vancomycin. May consider fecal microbiota transplantation or the monoclonal

antibody bezlotoxumab

Norovirus

Norovirus is the second most common cause of diarrhea (after *C. difficile*) among solid organ transplant recipients.

- Can cause both acute and chronic diarrhea (associated with relapsing and remitting episodes of diarrhea that may last for months to years)
- Diagnostic testing: norovirus PCR
- Treatment: supportive (volume repletion, antimotility agents), reduction in immunosuppression (inconclusive evidence). Nitazoxanide and IVIG are used for intractable or chronic relapsing diarrhea with variable results (anecdotal case reports).

Cytomegalovirus

- Diagnostic testing: plasma CMV PCR; colonoscopy may be required for diagnosis.
- Treatment (see also "Cytomegalovirus" section)

Other pathogens: bacterial (*Salmonella*, *Campylobacter*); parasitic infections (*Giardia*, *Cryptosporidium*, *Strongyloides*)

- Detected by stool culture, bacterial PCR panel, parasite-specific antigen testing, or ova and parasite exam
- Cryptosporidium may result in very high tacrolimus levels.

Common GI Infections

Posttransplant infections of the GI tract may be viral, fungal, or bacterial in etiology.

Common viral infections: CMV, HSV

Common opportunistic fungal infection: *Candida*

Common bacterial pathogens: *Clostridium difficile*, *Helicobacter pylori*

Helicobacter pylori

- Clinical disease spectrum of *Helicobacter pylori* includes chronic gastritis, duodenal and gastric ulcers, mucosa-associated lymphatic tissue (MALT) lymphoma, and gastric carcinoma.
- Treatment includes a triple-drug regimen consisting of two antibiotics and an acid-suppressive agent such as an H_2-blocker or a PPI. CNI and mTOR inhibitor drug levels should be monitored closely in patients receiving drug combination therapy that includes clarithromycin (see **Table 9.13**).
- In kidney transplant recipients infected with *H. pylori*, MALT lymphoma may be less aggressive than other lymphomas, and the disorder may be cured by eradication of *H. pylori*.

Routine Donor Screening for Infectious Disease

Deceased donor testing

- Blood and urine cultures
- Test all donors within 96 hours prior to organ procurement for:
  - HIV: Nucleic acid test (NAT) and either anti-HIV or HIV Ab/Ag
  - HBV: NAT, total anti-HBc, and HBsAg
  - HCV: NAT and anti-HCV
- Cytomegalovirus antibody (anti-CMV IgG)
- Epstein-Barr virus antibody (anti-EBV)
- Syphilis screening
- Donor screening in endemic settings: TB, strongyloides, West Niles virus
- HIV RNA by NAT or HIV-1/2 antigen/antibody fourth generation with reflex confirmation
- Toxoplasma immunoglobulin G (IgG) antibody test

Living donor testing (discussed under Living Donor evaluation)

Posttransplantation Serology Monitoring

- Test all recipients 4 to 8 weeks after transplant for HIV, HBV, and HCV using NAT (**Table 9.22**).

- In the event a recipient seroconverts, a treatment plan will be developed by the transplant team in conjunction with transplant infectious disease consultation.

Table 9.22 UNOS protocol surveillance for kidney transplant recipients

Pretransplant	Posttransplant
At baseline • Any CDC-approved HIV testing modality • HBsAg • HCV quantitative PCR	At 4-8 wk posttransplant • HIV RNA quantitative PCR • HBV DNA quantitative PCR • HCV RNA quantitative PCR At 12 mo posttransplant (for liver transplant recipients only) • HBsAg or HBV NAT, anti-HBsAb, and anti-HBcAb

Abbreviations: CDC, Centers for Disease Control; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; NAT, nucleic acid testing; PCR, polymerase chain reaction; UNOS, United Network for Organ Sharing.

Data from United Network for Organ Sharing. New OPTN policies to align with updated U.S. public health service guideline. January 20, 2021.

NONINFECTIOUS COMPLICATIONS AFTER KIDNEY TRANSPLANT

Surgical Complications (Usually Occur Early After Transplantation)

Wound infections

- Obese transplant recipients are at increased risk.
- mTOR inhibitors may delay wound healing and increase the incidence of lymphocele formation. Its use should be avoided in the early posttransplantation period.

Perinephric fluid collections

Lymphoceles

- Most common type of peritransplant fluid collection
- Usually occur several weeks to months after surgery

- Incidence is higher with mTOR inhibitors.
- Small lymphoceles are usually asymptomatic (conservative management) but larger lymphoceles can cause obstruction.
- Management includes percutaneous drainage or surgical repair.

Hematomas

- Usually occur in the immediate postoperative period
- May be external or subcapsular, usually resolve spontaneously
- May occur after allograft biopsy

Urinomas (urine leak)

- Clinical manifestations: Patients may present with pain over the allograft or abdominal pain (often severe), with or without scrotal pain or swelling, increasing wound drainage (clear fluid), and decreasing urine output. If a surgical drain is present, rising serous output may indicate a urine leak.
- Diagnosis: Measure both creatinine concentration in drain fluid (or fluid drained from the incision) and SCr: Surgical drain fluid with creatinine concentration of at least 1.5 to 2 mg/dL greater than that measured for serum is suggestive of a urine leak, although drain fluid values are often greater than 20 mg/dL in high-volume urine leaks. Diagnosis may be confirmed with a computed tomography (CT) cystogram, plain film cystogram, or voiding cystourethrogram (VCUG) demonstrating urine extravasation.
- Management: A Foley catheter should be immediately placed if there is a clinical suspicion of a urine leak. The catheter reduces intravesical pressure and may occasionally reduce or stop the leakage. Low-volume urine leaks (low drain output, minimal extravasation on cystogram) may be successfully managed with prolonged ureteral stenting and Foley catheter drainage (typically 1-3 weeks). A repeat cystogram should be performed to confirm resolution of the leak prior to catheter removal. High-volume leaks should be explored and ureteral reimplantation or other urinary reconstruction performed.

Obstructive uropathy

- **Etiologies**: ureteral blood clots, stones, ureteral kinking, neurogenic bladder, benign prostatic hypertrophy causing bladder outlet obstruction, ureteral strictures due to ischemia or BKPyV infection

Medical Complications (May Occur Early or Late After Transplantation)

Posttransplantation allograft dysfunction

The differential diagnosis of allograft dysfunction during various posttransplantation periods is summarized in **Table 9.23**.

Table 9.23 Differential diagnosis of allograft dysfunction during various posttransplantation periods

	First posttransplantation week: postoperative days 0-7	Early posttransplantation period: week 1 to 3 mo	Late posttransplantation period: >3 mo
Prerenal	• Volume loss (post-ATN diuresis, blood/GI loss) • Hypotension/overly aggressive BP treatment • Drug-induced renovasoconstriction (CNI, radiocontrast) • Others: acute cardiopulmonary event, intra-abdominal hypertension (volume overload, bowel edema/ischemia, severe constipation, obesity)	• Volume loss (see first posttransplant week) • Drug-induced and infectious causes of diarrheal fluid loss • Hypotension or overly aggressive BP treatment • Drug-induced intrarenal renovasoconstriction • Others: acute cardiopulmonary event, hypercalcemia	• Prerenal causes of AKI in the late posttransplant period mirror those found in the general population. • Drug-induced and infectious causes of diarrheal fluid loss
Intrinsic renal	• Posttransplant ATN (most common cause of DGF)	• Posttransplant ATN (most common biopsy findings in the early	• Late acute rejection (may be seen with medication nonadherence,

	First posttransplantation week: postoperative days 0-7	Early posttransplantation period: week 1 to 3 mo	Late posttransplantation period: >3 mo
	• CNI toxicity • Acute rejection • Recurrent disease: FSGS, atypical HUS (Early preemptive and long-term eculizumab or ravulizumab therapy may prevent atypical HUS recurrence.) • TMA of various etiologies (associated with recurrence of atypical HUS, CNI or mTOR inhibitors, and acute antibody-mediated rejection among others. Differential diagnosis of TMA is discussed in chapter 7.)	posttransplantation period) • CNI toxicity • Acute rejection • Recurrent disease: FSGS, atypical HUS • TMA of various etiologies (eg, CNI induced, de novo or recurrent atypical HUS, TMA of donor origin)	reduction in immunosuppression for specific indications, or the introduction of new medications that result in a reduction in CNI levels) • Both immunologic and nonimmunologic factors have been suggested to play an interactive role in the development of chronic progressive allograft dysfunction and graft loss (see **Table 9.27**). • Chronic rejection (AMR, TCMR, mixed rejection) • Recurrent glomerulonephritis (see **Table 9.28**) • BKPyV nephropathy • PTLD (for histopathologic findings, see **Figure 9.15**) • Chronic CNI toxicity
Postrenal (urinary tract obstruction)	**Structural** Intrinsic: • Ureter (blood clots, edema, ureteric stricture, or complications at	• The causes of postrenal obstruction in the early posttransplant period mirror those found in the first postoperative week	• BPH with outflow tract obstruction • Neurogenic bladder • BKPyV-associated ureteral stricture

	First posttransplantation week: postoperative days 0-7	Early posttransplantation period: week 1 to 3 mo	Late posttransplantation period: >3 mo
	ureteric anastomotic site) • Bladder (atrophic bladder associated with chronic anuric state in association with poor emptying) • Urethra (same causes as ureteral obstruction, urethral stricture, trauma from Foley insertion) Extrinsic: • BPH with outflow tract obstruction • Lymphocele • Large hematomas **Functional** • Pediatric-en-bloc kidneys (flow related) • Neurogenic bladder • Severe polyuria (underlying diabetes insipidus unmasked by a functioning graft) **Miscellaneous** • Ureteral kinking or ischemic injury	• Others: BKPyV-associated ureteral stricture	
Vascular	• Renal arterial thrombosis • Renal vein thrombosis	• Arterial or venous thrombosis generally occurs within the first week but may occur as long as 2 mo posttransplant.	Transplant renal artery stenosis

	First posttransplantation week: postoperative days 0-7	Early posttransplantation period: week 1 to 3 mo	Late posttransplantation period: >3 mo
		• Transplant renal artery stenosis	

Abbreviations: AKI, acute kidney injury; AMR, antibody-mediated rejection; ATN, acute tubular necrosis; BP, blood pressure; BPH, benign prostatic hypertrophy; CNI, calcineurin inhibitor; DGF, delayed graft function; FSGS, focal segmental glomerulosclerosis; GI, gastrointestinal; HUS, hemolytic uremic syndrome; mTOR, mammalian target of rapamycin;PTLD, posttransplantation lymphoproliferative disease; TCMR, T-cell mediated rejection; TMA, thrombotic microangiopathy.

Posttransplantation cardiovascular disease

Posttransplantation cardiovascular disease is the most frequent cause of death with a functioning graft:

Conventional risk factors: family history, pretransplant diabetes, male gender, age, White race, HTN, dyslipidemia, obesity, smoking

Unconventional or transplant-related risk factors: posttransplantation diabetes mellitus (PTDM), anemia, proteinuria, impaired graft function, low albumin, hyperuricemia, left ventricular hypertrophy

Posttransplantation HTN

Recipient-related risk factors: preexisting HTN, high body mass index or excess weight gain, sodium intake after transplantation, corticosteroids, cyclosporine, and to a lesser degree, tacrolimus. Excess renin output from the native kidneys may play a contributory role in some patients.

Donor-related factors: donor age, HTN, and donor family history of HTN. Donor factors associated with reduced graft function may indirectly increase posttransplantation HTN risk (eg, donor APOL-1 or CYP3A5 gene variants. The former is associated with early graft failure and the latter with CNI nephrotoxicity).

Kidney allograft-related factors: DGF, chronic allograft injury, acute rejection episodes, recurrent or de novo glomerulonephritis, transplant renal artery stenosis

Management of posttransplantation HTN

- The KDIGO guidelines suggest a BP goal of less than 130/80 mm Hg using standardized office BP measurements.
- A BP goal of less than 125/75 mm Hg for patients with proteinuria is of uncertain benefit.
- The 2021 KDIGO Clinical Practice Guidelines recommend a dihydropyridine CCB or an angiotensin receptor blocker (ARB) as first-line antihypertensive agent in adult kidney transplant recipients (1C). Rating interpretation: *Strength of recommendations*: Level 1 indicates "strong"; *Quality of supporting evidence*: Grade C indicates the true effect may be substantially different from the estimate of the effect. Adequately powered randomized controlled trial (RCT) to evaluate cardiovascular (CV) and kidney effects of ARB versus dihydropyridine CCB among kidney transplant recipients is needed.
- Currently available literature shows no conclusive evidence to suggest that one class of antihypertensive agents is superior to another in the transplant setting. Treatment should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions with immunosuppressive agents. Nondihydropyridine CCBs increase CNI blood levels and permit CNI dose reduction.
- Potential advantages and disadvantages of different classes of antihypertensive agents in kidney transplant recipients are shown in **Table 9.24**.

Table 9.24 Potential advantages and disadvantages of different classes of antihypertensive agents

Classes of drugs	Advantages/beneficial effects	Disadvantages/adverse effects
Angiotensin-converting enzyme (ACE) inhibitors Angiotensin receptor blockers (ARB)[a]	Beneficial in patients with proteinuria, DM, LVH Potential renoprotective and cardioprotective effects Beneficial in posttransplantation erythrocytosis Losartan may lower serum uric acid levels.[b]	Potentially worsening anemia GFR decline, hyperkalemia

Classes of drugs	Advantages/beneficial effects	Disadvantages/adverse effects
Mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone)	Improve outcomes in patients with HFrEF. May improve blood pressure control in difficult-to-treat hypertension	Severe hyperkalemia when used in combination with ACE inhibitor or ARB, particularly in patients with poor kidney function
α-Blockers (eg, prazosin)	Beneficial in patients with benign prostatic hypertrophy or neurogenic bladder	Orthostatic hypotension
β-Blockers (eg, carvedilol, metoprolol, bisoprolol)	Beneficial in patients with CAD or ischemic heart disease	Blunting of hypoglycemic unawareness, erectile dysfunction, hyperlipidemia, hyperkalemia (nonselective > selective β_1-blockers), bronchospasm
Calcium channel blockers Nondihydropyridine: diltiazem, verapamil. Dihydropyridine[a]: amlodipine, nifedipine	Ameliorate CNI-induced vasoconstriction Diltiazem may permit CNI dose reduction by up to 40%, verapamil by 30%-50%.	Increased risk of bradycardia when used with β-blockers (verapamil > diltiazem) Nifedipine, amlodipine (peripheral edema) Nifedipine (reflex tachycardia)
Central α-agonists (eg, clonidine, methyldopa)	Beneficial in patients with diabetic autonomic dysfunction	Depression
Diuretics (loop and thiazide)	Beneficial in patients who are volume expanded Thiazide may improve hyperkalemia commonly seen in CNI-treated patients. Its use may also increase BMD and decrease fracture risk (beneficial in osteoporosis).	Thiazides may be effective up to stage 4 CKD (Chlorthalidone)
Direct vasodilators (eg, hydralazine, minoxidil)	Minoxidil: may be beneficial in difficult-to-treat hypertension Hydralazine/nitrates combination therapy is recommended as add-on therapy among African Americans with HFrEF and NYHA III-IV despite ARNi/ACEi	Minoxidil (peripheral edema, reflex tachycardia, hirsutism), hydralazine (lupus syndrome and anti-neutrophilic cytoplasmic antibody [ANCA] vasculitis)

Classes of drugs	Advantages/beneficial effects	Disadvantages/adverse effects
	or ARB, mineralocorticoid receptor antagonist, SGLT2 inhibitor, and β blocker therapy.	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitor; BMD, bone marrow density; CAD, coronary artery disease; CKD, chronic kidney disease; CNI, calcineurin inhibitor; DM, diabetes mellitus; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor.

[a]The 2021 KDIGO Clinical Practice Guidelines recommend ARB or dihydropyridine CCB as first-line antihypertensive agent in adult kidney transplant recipients (see text).

[b]May be beneficial in patients with gout.

Posttransplantation dyslipidemia

Posttransplantation dyslipidemia is common after transplantation.

Risk factors

- Immunosuppressive agents: corticosteroids, cyclosporine, and to a lesser extent, tacrolimus, and the mTOR inhibitors sirolimus and everolimus
- Of all immunosuppressive agents, mTOR inhibitors are associated with the worst lipid profiles. Severe hypertriglyceridemia may occur with the use of sirolimus and everolimus due to decreased catabolism of apoB-100-containing lipoproteins (dose dependent, generally reversible upon discontinuation of mTOR inhibitors).
- Others: age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, genetic predisposition, β-blockers, diuretics

PTDM, formerly known as new-onset diabetes after transplantation (NODAT)

- In 2014, the International Expert Panel recommended changing the terminology NODAT back to PTDM, excluding transient posttransplantation hyperglycemia (transient is defined as posttransplant days 0-45).

- The diagnostic criteria for PTDM and prediabetes should follow those set forth by the American Diabetes Association expert panel (**Table 9.25**).
- PTDM has variably been shown to have an adverse impact on patient and graft survival.

Table 9.25 The American Diabetes Association diagnostic criteria for prediabetes and diabetes

Diagnostic test/criteria	Normoglycemia (mg/dL)	Prediabetes IFG or IGT (mg/dL)	Diabetes (mg/dL)
Casual plasma glucose with diabetic symptoms[a]			>200
Fasting plasma glucose	<100	100-125[b]	≥126
Oral glucose tolerance test	<140	140-199[b]	≥200
HbA_{1C}		5.7%-6.4%[b]	≥6.5%

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

[a]Diabetic symptoms defined as polyuria, polydipsia, weight loss. In the absence of unequivocal hyperglycemia, diagnosis should be confirmed by repeat testing on a different day.

[b]The risk is continuous and becomes disproportionately greater at higher glucose or A1C levels.

Data from American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36 suppl 1(suppl 1):S67-S74. doi:10.2337/dc13-S067

Risk factors

- PTDM may arise from both transplant-related and traditional risk factors.
- Diabetogenic immunosuppressive agents: corticosteroids, CNIs (tacrolimus > cyclosporine), mTOR inhibitors
- Non-diabetogenic agents: AZA, MPA derivatives (MMF, mycophenolate sodium), belatacept
- Risk factors for PTDM are summarized in **Table 9.26**. They may be loosely categorized into those that are nonmodifiable, potentially modifiable, and modifiable.

Table 9.26 Risk factors for posttransplantation diabetes mellitus (PTDM)

Nonmodifiable	Potentially modifiable	Modifiable
• African American, Hispanic • Age >40-45 y • Male recipient • Family history of DM • Gestational diabetes • HLA mismatches • HLA A30, B27, B42 • Acute rejection history • APKD[a] • Genetic polymorphism • Deceased donor • Male donor • Genetic polymorphism (eg, TCF7L2 variant [rs7903146], HNF-4A, insulin receptor substrate-1)	• Hepatitis C[b] • Cytomegalovirus[c] • Pretransplant IGT/IFG • Proteinuria[a] • Hypomagnesemia[d]	• Manipulation of immunosuppression (Clinicians must be familiar with patient's immune history.)[e] • Obesity (BMI ≥30 kg/m^2) or other component of the metabolic syndrome • Vitamin D deficiency

Abbreviations: APKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CMV, cytomegalovirus; DM, diabetes mellitus; HLA, human leukocyte antigen; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

[a]The association between proteinuria (and polycystic kidney disease) and PTDM has not been consistently observed.

[b]Curative therapy for chronic hepatitis C can now be achieved with highly effective direct-acting antiviral (DAA) agents (see also "Hepatitis C" section). Stable transplant recipients with HCV viremia by PCR should be referred to Hepatology for treatment. In HCV-positive kidney transplant candidates with a living donor, pretransplant treatment of HCV infection should be considered.

[c]For CMV prophylaxis therapy, please refer to **Table 9.21**.

[d]Persistent hypomagnesemia can occasionally be seen despite aggressive replacement therapy because of ongoing calcineurin inhibitor-induced urinary magnesium wasting.

[e]Manipulation of immunosuppression should be weighed against the risk of acute rejection.

Anemia

- Peri- or early postoperative period: dilutional anemia due to aggressive volume expansion, surgical postoperative bleeding

- Mild anemia is common in the early postoperative period when ESA (erythropoietin [EPO]-stimulating agent) is discontinued but usually improves within several weeks.
- Drug induced: MMF, sirolimus, everolimus, AZA, angiotensin-converting enzyme inhibitors (ACEIs), ARBs, dapsone
- Sirolimus inhibits erythropoiesis at the level of the EPO receptor.
- Other etiologic factors: iron deficiency, impaired graft function, acute rejection episodes

Posttransplant erythrocytosis (PTE)

- Defined as persistently elevated hematocrit (Hct) greater than 51% or hemoglobin (Hb) greater than 17 g/dL after transplant. Hct and Hb thresholds to define PTE may differ among centers due to differences in institutional reference range (and age- and gender-adjusted Hct and Hb levels).
- Incidence appears to have decreased to less than 10%, ascribed to more frequent use of ACEIs and ARBs.
- May develop within the first 2 years posttransplant (usually between 8 and 24 months) and generally affects those with good allograft function
- Spontaneous remission within 2 years of onset is observed in one-fourth of patients and may persist for several years in others.

Risk factors: presence of native kidneys, younger age, male gender, absence of rejection episodes, high baseline Hb before transplant, sodium-glucose cotransporter-2 (SGLT2) inhibitor use, HTN, dialysis vintage, and PKD and glomerulonephritis as the cause of ESKD. Transplant renal artery stenosis has not consistently been shown to be a risk factor for PTE.

Management

- The Hb/Hct threshold for treatment may vary depending on gender and institutional reference range. Generally, treatment is recommended for Hb levels exceeding 17 to 18 g/dL or Hct levels greater than 51% to 54% because of the associated risk of thromboembolic complications, HTN, and headaches.

- Treatment with ACEIs or ARBs is often sufficient. Relapse is common and often necessitates long-term ACEI or ARB treatment.
- Phlebotomy may be considered in severe PTE after optimization/treatment of any associated hypoxia-driven PTE.
- Low-dose aspirin 81 mg daily may be considered if there is no contraindication.

Persistent PTE or PTE occurring late after transplant warrants further evaluation to exclude:

- Erythropoietin-producing neoplasms, for example, renal cell carcinoma (RCC) in the native or transplanted kidneys, hepatocellular carcinoma, cerebellar hemangioblastoma. Imaging studies of the allograft and native kidneys should be performed particularly when RCC risk factors are present (eg, pretransplant increased dialysis duration or known acquired cystic kidney disease).
- EPO-producing kidney disease/disorder: APKD, hydronephrosis, renal artery stenosis
- Hypoxemia-associated increased EPO production: sleep apnea, high altitude, chronic pulmonary disease
- Drug related: use of androgen, anabolic steroids, or surreptitious exogenous ESA
- Hemoconcentration associated with diuretic use

Posttransplantation proteinuria

- Occurs in 9% to 40% of kidney transplant recipients with a functioning graft (wide range reported due in part to the threshold used to define proteinuria and time after transplantation)
- Proteinuria from native kidneys typically decreases rapidly after transplantation and resolves within 3 months (generally within the first month) after transplant.

Screening

- Urine-protein-to-creatinine ratio and urine-albumin-to-creatinine ratio are reasonable screening tests at each clinic visit.
- Significant proteinuria warrants confirmation with 24-hour urine collection (although seldom performed in clinical practice).

Etiologies: recurrent disease particularly primary FSGS, secondary FSGS, transplant glomerulopathy (TG), acute allograft rejection (proteinuria usually <500 mg/dL but higher levels may be seen), mTOR inhibitor use (with or without association with FSGS), and chronic CNI nephrotoxicity. Proteinuria has also been reported to be associated with de novo DSA detection.

Clinical significance of posttransplantation proteinuria

- Persistent or worsening proteinuria is usually indicative of allograft pathology.
- As in the nontransplant setting, posttransplantation proteinuria increases the risk of cardiovascular events, graft loss, mortality, and PTDM.

Management

- An allograft biopsy should be performed in patients with persistent or worsening proteinuria and in those whose primary kidney disease is FSGS to monitor for disease recurrence.
- The use of ACEI or ARB: The favorable effect of ACEI or ARB on patient and graft survival has not been consistently demonstrated. Nonetheless, ACEI or ARB should be considered in transplant recipients with proteinuria because of their well-established antiproteinuric and cardioprotective effects.

Chronic allograft injury

Both immunologic and nonimmunologic factors have been suggested to play an interactive role in the development of chronic allograft injury and graft loss. These may include:

- Chronic antibody-mediated, chronic cell-mediated rejection, or both
- Recurrent glomerular disease
- BKPyV-nephropathy
- Posttransplantation lymphoproliferative disorder (PTLD)
- Chronic CNI nephrotoxicity, among others
- Suggested immunologic and nonimmunologic causes of chronic allograft injury are listed in **Table 9.27**.

Table 9.27 Alloimmune and non-alloimmune causes of chronic allograft dysfunction

Alloimmune causes	Non-alloimmune causes include but not limited to the following factors
Chronic antibody-mediated rejection (AMR)	Chronic CNI toxicity
Chronic T-cell-mediated rejection (TCMR)	Chronic hypertension
Mixed chronic AMR and TCMR	Hyperlipidemia
	Viral infection (BKPyV)
	Chronic bacterial pyelonephritis
	Recurrent or de novo diabetic changes
	Recurrent or de novo glomerular disease
	Posttransplant lymphoproliferative disorder
	Marginal donor kidneys (eg, preimplantation glomerulosclerosis and IFTA, long cold and/or warm ischemia times with suboptimal renal function recovery after transplant)

Abbreviations: BKPyV, BK polyomavirus; CMV, cytomegalovirus; CNI, calcineurin inhibitor; IFTA, interstitial fibrosis and tubular atrophy.

Recurrent diseases

- Clinicians MUST remain vigilant for the possibility of glomerular disease recurrence after transplantation.
- Patients should be counseled on the risk of disease recurrence and the risk of graft loss associated with disease recurrence.
- Specific glomerular disease recurrence and suggested treatment (when applicable) are summarized in **Table 9.28**.

Table 9.28 Recurrent disease after transplant and graft loss from disease recurrence

	Recurrence rate/incidence	Risk of graft loss	Comments/treatments
Primary glomerular disease			
Primary FSGS **Note:** Secondary FSGS does not recur if the underlying etiology leading to FSGS has been modified.	30%-60%	TANGO study,[a] *n* = 176 Graft loss among patients with vs those without recurrence over a median of 5 y: 39% vs 15% ANZA registry study, *n* = 736 (666 adults, 70 children). Graft loss at 5 y among patients with vs those without recurrence: 48% vs 17%	• May recur immediately or months to years after transplant. Up to 80% recurrence in the second graft if prior graft lost to recurrence, and almost 100% recurrence in the third graft • Risk factors: younger age at diagnosis, rapid progression to ESKD (<3 y), White race, severe proteinuria (60% recurrence) • Monogenic or familial FSGS has low recurrence rate (0% in large pediatric cohorts). Exception: NPHS1 mutation (Fin-major type) has a recurrence rate of 25%-34%. • APOL1 high-risk variants should not recur after transplant. • Histologic variants (collapsing, tip lesion, cellular, perihilar, not otherwise specified) have no effect on recurrence risk. • **Treatment:** plasmapheresis (standard of care) with or without rituximab. Others (less well defined): abatacept, adrenocorticotropic hormone gel, adalimumab, LDL apheresis
IgA nephropathy	• 10%-30% (for-cause	TANGO study[b]:	• Incidence increases with time after transplant.

	Recurrence rate/incidence	Risk of graft loss	Comments/treatments
	biopsies) • 25%-53% (protocol biopsies)	Cumulative risk of recurrence increased after transplant and was associated with a 3.7-fold greater risk of graft loss.	• Appears to have no effect on short-term graft survival but in studies with longer-term follow-up, graft outcomes appear to be worse compared with patients without recurrence
Immune-complex mediated MPGN	25%-65%	10%-33%	• Recurrence risk varies depending on underlying etiology.
Fibrillary glomerulonephritis (FGN)	8%-50%	Up to 50% (based on small case series)	• Limited data[c] • FGN with monoclonal gammopathy is associated with high risk of recurrence and graft loss.
Membranous nephropathy[d] (MN)	3%-50%	5%-30%	• Often PLA2R positive, IgG4 dominant • Disappearance of anti-PLA2R at the time of transplant (10% recurrence) • Persistent anti-PLA2R Ab at the time of transplant (50% recurrence) • MN without ever having anti-PLA2R antibody in either serum or kidney biopsy (30% recurrence) • Treatment: RASi in all patients with posttransplant MN. Rituximab: If proteinuria >1,000 mg despite RASi. Some experts recommend rituximab regardless of anti-PLA2R levels.

	Recurrence rate/incidence	Risk of graft loss	Comments/treatments
C3 glomerulopathy • C3 GN • Dense deposit disease (DDD)	C3GN >50% DDD: 80%-100%	50%-100% (based on small case series)	• Consider eculizumab (or ravulizumab) for patients at high risk for graft loss (eg, high-grade or worsening proteinuria and/or progressive decline in graft function). Further studies are needed. • Monoclonal gammopathy-associated C3GN has a high rate of recurrence.
Associated with systemic disease			
Atypical HUS	25%-80%	40%-60%	• May be triggered by allograft rejection, endothelial injury, ischemia-reperfusion injury, infections (CMV, influenza, parvovirus B19, BKPyV, upper respiratory or GI infections) • Very high risk of recurrence in patients with mutations involving circulating factors (particularly complement factor H and factor I) • Mutation in membrane cofactor protein has low risk of recurrence unless it is associated with other mutations. • Treatment: eculizumab or ravulizumab[e]
Cryoglobulinemia	50%	Not available	
Monoclonal immunoglobulin deposition disease	50%	Not available	

	Recurrence rate/incidence	Risk of graft loss	Comments/treatments
ANCA-associated crescentic glomerulonephritis	9%-50%	Rare	• Less recurrence if in sustained remission before transplantation (sustained remission defined as at least 1 y before transplantation) • Recurrence rates have decreased in recent years, thought to be due to the use of more potent immunosuppressive agents.
Diabetic glomerulosclerosis	40%	17%-40%	
IgA vasculitis (HSP)	15%-60%	10%	
Lupus nephritis	2%-30%	<5%	May recur as nonspecific immune–complex disease
Ant-GBM antibody nephritis	Clinical recurrence is low.	50%	• De novo anti-GBM may develop after transplant in patients whose primary disease is Alport syndrome (particularly males with X-linked COL5A large deletional mutations).
Fabry disease	<5%		
Shiga-toxin-associated HUS	0%-10%		
Amyloidosis	20%-30%		**Secondary or AA amyloidosis** • Recurrence risk varies depending on whether the underlying cause of chronic inflammation can be controlled or eradicated.

	Recurrence rate/incidence	Risk of graft loss	Comments/treatments
			• Familial Mediterranean fever (FMF): Recurrence of amyloid deposition in the allograft is common. Colchicine may prevent the development of proteinuria. **Primary or AL amyloidosis** • Recurrence is likely if the patient is not in complete hematologic response at transplant. (Hematology/Oncology consultation is strongly recommended.)

Abbreviations: AA amyloidosis, amyloid A amyloidosis; AL amyloidosis, light-chain amyloidosis; AMR, antibody-mediated rejection; ANCA, antineutrophil cytoplasmic antibodies; ANZA, Australian and New Zealand Association; CMV, cytomegalovirus; DM, diabetes mellitus; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HCV, hepatitis C virus; HSP, Henoch-Schonlein purpura; HUS, hemolytic uremia syndrome; IgA, immunoglobulin A; IgG1, immunoglobulin G1; IgG4, immunoglobulin G4; LDL, low-density lipoprotein; MPGN, membranoproliferative glomerulonephritis; PLA2R, phospholipase A2 receptor; RASi, renin-angiotensin system inhibitors.

[a]The Post-Transplant Glomerular Disease (TANGO) study is an **observational, multicenter, international cohort study** that aims to investigate glomerular disease recurrence posttransplantation.

[b]Interested readers are referred to Uffing A, Pérez-Saéz MJ, Jouve T, et al. Recurrence of IgA nephropathy after kidney transplantation in adults. *Clin J Am Soc Nephrol*. 2021;16(8):1247-1255.

[c]In a series of 13 patients with FGN who received 13 renal transplants, 1 of 13 (8%) had recurrent FGN (ANZDATA registry cases).

[d]Pretransplant: Monitor serum PLA2R Ab at the time of transplant evaluation and at the time of transplant. Posttransplant: Monitor PLA2R levels every 3 to 6 months in patients with stable PLA2R-associated MN. [e]other agent in clinical trial: iptacopan, a complement factor B inhibitor.

Primary hyperoxaluria type 1 (PH1)

- Lack of liver enzyme-specific peroxisomal enzyme alanine-glyoxylate aminotransferase in patients with PH1 results in decreased transamination of glyoxylate to glycine and increased production of oxalate and glycolate. Because oxalate is eliminated unaltered by

renal excretion, isolated kidney transplantation can result in rapid deposition of oxalate in the allograft and subsequent stone formation, nephrocalcinosis, and graft failure. Liver transplantation corrects the underlying hepatic-based metabolic disorder. Hence, in patients with ESKD due to PH1, SLKT is recommended.

- Whether novel RNA interference (RNAi) therapy targeting hepatic enzymes to modulate oxalate production improves outcomes in patients with PH1 and permits isolated kidney transplantation is a subject of ongoing clinical research (FDA-approved RNAi therapy: lumasiran, nedosiran). Discussion is beyond the scope of this chapter.

Allograft failure

The management of an allograft failure includes consideration for dialysis reinitiation, tapering/discontinuation of immunosuppressive therapy, and consideration for retransplantation.

Timing of dialysis reinitiation

- Currently there is no consensus on the timing of dialysis reinitiation after a failed transplant. In general, dialysis reinitiation should be based on traditional clinical and/or laboratory parameters and patient's overall wellness (or lack thereof, eg, symptomatic uremia, volume overload or hyperkalemia refractory to medical treatment, and/or malnourishment, among others).
- Timely referral for vascular access placement in patients without a functioning arteriovenous fistula or arteriovenous graft at the time of graft failure is recommended.

Immunosuppression management

- Consensus guidelines for the management of immunosuppression in patients with a failed allograft are lacking. Interested readers are referred to Pham PT, Lum EL, Pham PC. Management of patients with a failed transplant. In: Pham PT, Pham PC, eds. *Quick Guide to Kidney Transplantation: From Initial Evaluation to Long-Term Posttransplant Care*. Wolters Kluwer; 2020 for suggested immunosuppression withdrawal protocols.

- Immunosuppression is typically discontinued following allograft nephrectomy unless there is a concern for allosensitization in retransplant candidate with a potential living donor.
- Although evidence-based recommendations are lacking, continuation of low-dose immunosuppression may be appropriate in the following settings:
  - Patients with kidney disease who have not yet started dialysis
  - Dialysis dependent with residual urine output greater than 300 to 500 mL/d (case-by-case basis)
  - Patients with symptomatic rejection or graft intolerance syndrome to serve as a bridge to allograft nephrectomy
  - Patients with anticipated living donor re-allograft transplant or those anticipated to have a short wait time after early relisting to prevent allosensitization

Retransplantation consideration

In potential re-allograft candidates, blood transfusion should be avoided unless absolutely necessary to prevent allosensitization.

Graft intolerance syndrome

- Commonly occurs within the first year of returning to dialysis
- May occur in 30% to 50% of patients despite different immunosuppression withdrawal protocols

Clinical manifestations: fever, malaise, gross hematuria, graft enlargement or tenderness, unexplained fatigue, and/or flu-like symptoms

Laboratory findings (not invariably present): hypoalbuminemia, anemia resistant to ESA, elevated inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and ferritin

Management

- Symptoms may respond to temporary intensification of immunosuppression, usually in the form of intravenous corticosteroid pulse.
- Recurrent episodes of graft intolerance syndrome generally require allograft nephrectomy. Repeated courses of pulse corticosteroid

therapy are not recommended.

POSTTRANSPLANTATION BONE AND MINERAL DISORDER

Hypophosphatemia

- Hypophosphatemia can be seen in 40% to 90% of patients after transplant. The majority of cases are mild to moderate (serum phosphorous >1.5 to <2.3 mg/dL).
- Hypophosphatemia is most pronounced within the first 3 months posttransplant and generally recovers to normal levels by 1 year (typically improves in approximately 86% of patients by 12 months). Beyond the first year after transplant, some patients continue to experience urinary phosphate wasting despite normalization of parathyroid hormone levels.
- Concomitant hypercalcemia suggests posttransplantation hyperparathyroidism.
- In the absence of hypercalcemia, renal phosphate wasting syndrome or malnutrition should be considered.

Etiologies of posttransplantation hypophosphatemia

Renal phosphate wasting may occur due to residual high serum levels of the bone-derived phosphaturic hormone fibroblast growth factor 23 (FGF23) and secondary or tertiary hyperparathyroidism in the pretransplant setting. In recipients of a successful kidney allograft, FGF23 levels gradually decrease in the first few months after transplant and typically normalize (or decrease to concentration levels comparable to their CKD counterparts) within the first year, but high parathyroid hormone (PTH) levels may persist longer.

Other contributors to hypophosphatemia

- Metabolic acidosis stimulates phosphaturia as phosphate serves as a titratable acid.
- Glucocorticoids inhibit intestinal sodium-phosphate transporter activity.

- mTOR inhibitors (sirolimus, everolimus) inhibit renal tubular phosphate reabsorption by a not well-defined mechanism.
- Early after transplantation, hypophosphatemia has been attributed to a massive initial diuresis, defective renal phosphate reabsorption due to ischemic injury, glucosuria (due to hyperglycemia-induced osmotic diuresis), and corticosteroid use (by inhibiting proximal tubular reabsorption of phosphate).

Treatment

- Mild to moderate hypophosphatemia is not likely to be associated with significant adverse symptoms and does not need to be treated.
- More pronounced hypophosphatemia may be associated with symptoms of muscle weakness.
- Serum phosphate level of 1.5 mg/dL (~0.5 mmol/L) has been suggested as the lower limit to consider initiation of oral phosphate replacement, as symptoms can develop below this level.
- Potential adverse effects of aggressive phosphorous supplementation: worsening existing hyperparathyroidism and elevated FGF23 levels, vascular and kidney allograft calcifications

Calcium

Serum calcium levels may follow a biphasic pattern with significant decline in the first 1 to 2 weeks posttransplant followed by a significant increase during the first 3 to 6 months after transplantation.

Hypocalcemia

Early posttransplant low calcium levels are associated with lower pretransplant parathyroid levels and may be associated with low bone turnover but may also be impacted by postsurgical early hypoalbuminemia and volume expansion.

Hypercalcemia

- Hypercalcemia is common after transplantation.

- Hypercalcemia is generally moderate with total calcium ranging between 10.5 and 11.5 mg/dL. Severe hypercalcemia (total calcium level >12 mg/dL) is uncommon.
- Hypercalcemia prevalence decreases over time. However, hypercalcemia can persist in as much as 15% of patients at 1 year after transplantation but generally ranges between 0.5% and 5.6%

Contributing factors

- Residual secondary or persistent tertiary hyperparathyroidism associated with ESKD prior to kidney transplantation
- Resolution of soft tissue calcifications and immobilization
- Vitamin D repletion
- The concomitant presence of severe hypophosphatemia particularly in patients with excellent graft function may exacerbate hypercalcemia through stimulation of renal proximal tubular 1α-hydroxylase.

Management

In kidney transplant recipients with hypercalcemic hyperparathyroidism, treatment with the calcimimetic cinacalcet can reduce serum calcium and PTH levels and improve hypophosphatemia.

Severe hypercalcemia or persistent hypercalcemia (≥12 months)

- Further evaluation is required.
- Initial assessment should include an intact PTH level.
- Neck ultrasound or preferably parathyroid technetium 99mTc-sestamibi scan is required to determine if the clinically observed hyperparathyroidism arises from parathyroid adenoma or parathyroid gland hyperplasia, or hyperplastic nodular formation of the parathyroid glands.

Hyperparathyroidism

- Secondary hyperparathyroidism improves after kidney transplantation with good allograft function with progressive decrease in PTH levels in the first 3 to 6 months.

- Involution of parathyroid hyperplasia occurs very slowly and is associated with persistent hyperparathyroidism.
  - 50% of recipients continue to have elevated PTH levels at 1-year posttransplant.
  - Longer-term follow-up has shown that only approximately 25% of recipients have normal PTH levels and 25% continue to have elevated PTH levels greater than twice the normal at 5 years after transplantation.

Risk factors for persistent posttransplantation hyperparathyroidism

- Time on dialysis more than 6 years, calcium-phosphate product of greater than 55 (mg/dL), cinacalcet use prior to transplant
- Others: higher pretransplant PTH levels, larger gland size and presence of multinodular hyperplasia, persistent elevation of alkaline phosphatase, poor allograft function, low vitamin D levels

Adverse effects associated with persistent hyperparathyroidism: hypercalcemia, development or exacerbation of osteopenia/osteoporosis, fractures, allograft dysfunction, renal calcinosis, vascular calcifications, increased risk of cardiovascular event

Treatment

- Clinically significant hypercalcemia due to persistent (tertiary) hyperparathyroidism after transplantation may be managed medically (calcium-sensing receptor agonist) or surgically (parathyroidectomy).
- The use of cinacalcet for the treatment of hypercalcemia after transplant is off-label and has not been approved for this indication by the FDA.
- Parathyroidectomy: Observational studies of parathyroidectomy in kidney transplant recipients for persistent (tertiary) hyperparathyroidism show high success rates in resolving hyperparathyroidism with subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Limited glandular resection (of only one or two macroscopically enlarged glands) is associated with significant risk of recurrence of hyperparathyroidism.

- Choice of therapy (medical vs surgical): No specific guidelines dictating timing or goals of treatment exist due to lack of evidence supporting specific recommendations. Comparison of treatment outcomes and advantages and disadvantages of cinacalcet versus parathyroidectomy is summarized in **Table 9.29**. Opinion-based recommendations or considerations that may guide therapy based on available evidence and/or clinical situation include:

Table 9.29 Cinacalcet versus parathyroidectomy for hypercalcemia after transplant

	Cinacalcet	Parathyroidectomy
Control of hypercalcemia	80% of patients	90%-100% of patients
PTH normalization	Minority	Nearly all
Effect on BMD	• To date, no beneficial effect on bone density, fractures, vascular calcifications, or nephrocalcinosis has been demonstrated. • Off-label use (not approved by FDA for use in the treatment of posttransplantation hypercalcemia)	• Improved BMD • Parathyroidectomy is preferred over cinacalcet for long-term management of BMD such as persistent hypercalcemia, nephrocalcinosis, or high bone turnover.[a]
Potential adverse effects	Hypercalciuria	Surgical risks • Recurrent laryngeal nerve injury • Early and long-term hypocalcemia • Irreversible low bone turnover
Costs	Open-ended costs of therapy for indefinite duration	Cost equals to approximately 14 mo of cinacalcet therapy.

Abbreviations: BMD, bone marrow density; FDA, U.S. Food and Drug Administration; PTH, parathyroid hormone.

[a]Randomized controlled trial showed increased BMD femoral neck and reduction in bone resorption markers.

- Delaying treatment beyond 6 to 9 months after transplant since hypercalcemia and associated hyperparathyroidism may continue to abate during this time frame.
- Age and medical infirmity, as well as patient preference, may favor medical versus surgical treatment due to potential surgical risks.
- Hypercalcemia that is not controlled with calcimimetics may require parathyroidectomy.
- Symptomatic/progressive hypercalcemia: nephrolithiasis, persistent metabolic bone disease, calcium-related allograft dysfunction, progressive vascular calcification, calciphylaxis
- Cost of calcimimetics may impact treatment decisions.
- Treatment goal of improving low bone density may favor parathyroidectomy (beneficial effect on complications of vascular calcification complications unclear).
- Presence of multiple risk factors prior to transplant that significantly decreases the likelihood of avoiding complications of persistent hyperparathyroidism after transplant

Vitamin D Insufficiency or Deficiency

Calcidiol (25[OH]D) deficiency is common in transplant recipients and can persist for more than 1 year after transplantation.

- Approximately 80% are insufficient with levels less than 30 ng/mL.
- Up to 30% are deficient with levels less than 20 ng/mL.

Factors associated with calcidiol deficiency can include:

- Female sex, ethnicity (African Americans have high incidence of deficiency but this is associated with lower binding protein; active unbound form may be sufficient.)
- Malabsorption or malnutrition
- Seasonal variation
- Proteinuria and hypoalbuminemia can decrease levels of binding protein and lower total levels.

- Increased catabolism of calcidiol due to corticosteroids
- Reduced production from sterol precursors due to recommendations to limit ultraviolet (UV) light exposure to lower skin cancer risk after transplantation

Low calcidiol levels in transplant recipients may be associated with:

- Increased risk of chronic allograft nephropathy
- Increased risk of cardiovascular disease
- Increased risk of malignancy
- Increased risk of PTDM
- Elevated PTH levels and metabolic bone disease after transplant

Management

- KDIGO suggests correcting vitamin D deficiency in transplant recipients using treatment strategies recommended for the general population, and transplant recipients with advanced CKD and low bone marrow density (BMD) be managed according to nontransplant CKD recommendations.
- Calcitriol ($1,25[OH]_2D$) levels improve after transplantation and normalize in the majority of recipients by 3 to 6 months after transplantation. Increases in calcitriol levels are associated with:
  - 1α-Hydroxylase activation related to elevated PTH levels and hypophosphatemia
  - Decreased FGF23 levels after a successful transplant (1α-Hydroxylase is inhibited by high levels of FGF23.)

Posttransplantation Bone Disease

Specific bone diseases

Osteopenia/osteoporosis

- Posttransplant decline in BMD is most pronounced in the first 6 months and correlates with higher corticosteroid exposure. Note:

Osteopenia on bone density does not predict osteoporosis on bone biopsy.

- The early rapid decrease in BMD is usually followed by a slower rate of bone loss.
- Over the past decade, reduced corticosteroid exposure has been seen to be associated with lower fracture rates.

Avascular necrosis (AVN)

- Most commonly affects the femoral head and neck but may affect other joints including knees, shoulders, ankles, elbows, and wrists
- Risk factors: greater exposure to intravenous corticosteroid pulse therapy, low bone mass, increasing dialysis duration, excessive weight gain, dyslipidemia, microvascular thrombosis, and history of local trauma
- Early steroid withdrawal has been shown to reduce fracture risk.

Other bone diseases: adynamic bone disease, osteomalacia, and mixed bone disease

Prevention of bone complications

Goal: to reduce fracture risks. However, randomized studies of therapy for metabolic bone disease have shown benefits in terms of improved bone density but failed to show reduction in fracture risk end point.
Vitamin D has been suggested to improve bone density.

Biphosphonates

- Bisphosphonates should be used with caution in patients with impaired kidney function and avoided in CKD G4-G5.
- Pamidronate use has been reported to be associated with collapsing FSGS, noncollapsing FSGS, and minimal change disease (MCD).

Denosumab

- Denosumab is a humanized monoclonal antibody that binds to and prevents RANKL (receptor activator of nuclear factor-β ligand) from activating its receptor (RANK) on the surface of osteoclast and their precursors.
- Denosumab has been shown to increase BMD.

- Significant bone loss at the spine and hip may occur after discontinuation of denosumab.
- After discontinuation of denosumab, potent bisphosphonate therapy should be initiated and continue for several years (to preserve BMD and prevent vertebral fractures).

KDOQI guidelines

BMD testing recommended if the results will alter therapy.

- First 3-month posttransplant, eGFR of greater than 30 mL/min/1.73 m^2: Measuring BMD is suggested if patients receive corticosteroids or have risk factors for osteoporosis as in the general population **(2D)**.
- First 12-month posttransplant, eGFR of greater than 30 mL/min/1.73 m^2, and low BMD: Treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents may be considered.
- After the first 12 months: There are insufficient data to guide treatment **(2D)**.
- Other suggestions: Treatment choices may be influenced by the presence of CKD-mineral and bone disorder, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatase, and 25(OH)D **(2C)**. It is reasonable to consider a bone biopsy to guide treatment **(not graded)**.
- Note: KDIGO guideline recommendation ratings: Level 1 "we recommend"; Level 2 "we suggest"; Grade A: Quality of evidence is high; Grade B: Quality of evidence is moderate; Grade C: Quality of evidence is low; Grade D: Quality of evidence is very low.

POSTTRANSPLANTATION MALIGNANCY

Malignancy After Solid Organ Transplantation

- Recipients of organ transplants are at increased risk for developing certain neoplasms compared with the general population.
- Posttransplant malignancy is an important cause of death in long-term kidney transplant recipients.
- The overall incidence of de novo malignancies is 2- to 4-fold greater in solid organ transplant recipients compared with that of the

general population.

Specific cancers

- Compared with the general population, kidney transplant recipients have a substantially higher risk for:
  - Nonmelanoma skin cancers
  - Kaposi sarcoma
  - PTLD
  - Nonmelanoma skin cancers (particularly SCC) have the highest "standardized incidence ratios" (ratio of the observed number of cases to the expected number of cases) in transplant recipients.
- Common cancers in the general population, including breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some but not all studies.

Suggested risk factors

- Duration and intensity of immunosuppressive agents due to their presumed ability to promote replication of oncogenic viruses
- Infection-associated cancers:
  - Kaposi sarcoma and human herpes type 8
  - Non-Hodgkin lymphoma and EBV
  - Well-described viral-associated cancers are shown in **Table 9.30**.

Table 9.30 Viral-associated cancers

Oncogenic viruses	Specific viral-associated cancers
Epstein-Barr virus	PTLD, non-Hodgkin lymphomas, Hodgkin lymphoma, and plasma cell neoplasms
Human herpes virus 8	Kaposi sarcoma
Hepatitis B and hepatitis C	Hepatocellular carcinoma

Oncogenic viruses	Specific viral-associated cancers
Human papillomaviruses (HPV)	Vulva, vagina, cervix, penis, anus, oral cavity, and pharynx
Possibly HPV related	Non-melanocytic-related skin cancer

Abbreviation: PTLD, posttransplant lymphoproliferative disorder.

- The precise cause of increased risk of lip cancer has not been well defined. The Transplant Center Match Study database demonstrated a strong association of lip cancer with White race and prior history of skin cancer, suggesting that UV radiation exposure is an important risk factor. A higher incidence of lip cancer was also found among transplant recipients receiving cyclosporine/AZA compared with tacrolimus/MMF maintenance immunosuppression. The contributory role of cyclosporine and AZA was thought to be due to their photosensitizing or DNA-damaging effects.
- Although melanoma has no known infectious etiology, a causal relationship between immunosuppression and its development in recipients of kidney transplants has been suggested.
- Others: older age, male gender, White race, pretransplant dialysis duration, smoking history, deceased donor organ, cumulative exposure to radiation from repeated medical imaging studies, antecedent use of immunosuppressive agents to treat primary kidney diseases

Skin Cancers

- Most common de novo posttransplant malignancy in the adult transplant population
- Incidence of SCC is significantly higher than that of basal cell carcinoma (BCC).

SCC in organ transplant recipients

- Most common cutaneous malignancies in solid organ transplant recipients, with a 65- to 100-fold greater incidence compared with

the general population

- More clinically aggressive disease and worse tumor histology compared with that of the general population

Risk factors for skin cancers

- Pretransplant history of SCC
- Actinic keratoses and viral warts (increased risk for keratinocyte carcinoma)
- Duration of follow-up after transplant
- Light-skin color (easily sunburnt)
- Intensity of sun (UV radiation) exposure (eg, high-altitude residence)
- Older age at transplant
- Patients who develop SCC after transplantation are at increased risk for subsequent SCC, whereas those with a first posttransplant BCC are at risk for subsequent BCC.
- AZA-based immunosuppression was found to be associated with a significantly increased risk for subsequent SCC but not subsequent BCC.

NOTE

Voriconazole (once a commonly used antifungal agent to treat invasive fungal infection in organ transplantation) use is associated with increased cutaneous SCC risk in organ transplant recipients, particularly in recipients of lung transplants. Voriconazole's increased risk of skin malignancy has been suggested to be due to increased skin photosensitivity.

The use of mTOR inhibitors in posttransplant cutaneous malignancies

- The mTOR inhibitors sirolimus and everolimus have antiproliferative and antitumoral effects.
- Both "de novo" mTOR inhibitor use and CNI to mTOR inhibitor "conversion therapy" were found to be associated with decreased nonmelanoma skin cancer risks (see **Appendix A9.5**). Its use is effective in both primary and secondary skin cancer prevention.

Furthermore, the earlier the conversion after an initial diagnosis of cutaneous SCC, the greater the efficacy.

- Meta-analyses and randomized trials evaluating mTOR inhibitor use in secondary prevention of SCC showed a reduction in cumulative tumor load, suggesting that most benefit is gained by early conversion to an mTOR inhibitor-based maintenance regimen.
- It is suggested that the protective effect of mTOR inhibitors against skin cancer is a result of its inhibition of several UV-induced mechanisms involved in skin carcinogenesis.

Dermatology surveillance

The following guidelines are drawn from the evidence-based skin cancer surveillance program in the United Kingdom.

- High risk (age >55 years at transplant and light-skin color): annually for the first 2 years and then every 6 months thereafter
- Low risk (Asian or Black): every 2 years
- Increased surveillance is recommended after the first cancer.

Posttransplantation Lymphoproliferative Disorder (PTLD)

- PTLD encompasses a wide spectrum of lymphoid proliferations ranging from reactive polyclonal lesions to frank malignant monoclonal lymphomas.
- The WHO histologic classification of PTLD can be divided into four subtypes based on morphology, clonality, and molecular criteria:
  - Early lesions
  - Polymorphic PTLD
  - Monomorphic PTLD
  - Classical Hodgkin lymphoma-type PTLD

Epidemiology

- PTLD is the most common type of posttransplantation malignancy in children.

- PTLD is the second or third most common posttransplantation malignancy in adults (follows only nonmelanoma skin cancers and Kaposi sarcoma).
- Incidence varies with the type of organ transplanted.
  - Kidney (1%-2%), liver (1%-4%), simultaneous kidney pancreas (2%-3%), heart-, lung-, and heart lung transplants (2%-10%), small bowel and multivisceral transplantation (up to 33%)
  - The high incidence of PTLD in intestinal and multiorgan transplants has been attributed to the use of more intensive immunosuppression and the amount of donor-derived lymphoid tissue transferred at organ transplantation.
- The majority of PTLD are non-Hodgkin lymphoma of B-cell origin and are CD20-positive.

Pathogenesis

Although PTLD was originally thought to be uniformly linked to EBV infection, an increased incidence of EBV-negative PTLD has been reported. In some series, EBV-negative PTLD may occur in up to 30% to 50% of cases. EBV-associated PTLD appears to vary with PTLD subtypes. Interested readers are referred to **Appendix A9.6.**

EBV-positive versus EBV-negative PTLD

- EBV-positive PTLD is typically considered to result from EBV infection of recipient B cells but may be of donor origin.
  - In immunocompetent hosts, EBV-specific CD8+ effector and memory T cells are responsible for controlling EBV-infected B cells from uncontrolled proliferation and transformation.
  - Immunosuppression-related decrease in T-cell immune surveillance in transplant recipients has been suggested to play a major contributory role in EBV-positive PTLD.
- The pathogenesis of EBV-negative PTLD remains speculative.
  - Proposed hypotheses of EBV-negative PTLD include hit-and-run EBV infection (disappearance of EBV following an initial infection that leads to PTLD), viral infection other than EBV (eg, CMV), persistent antigen stimulation by the graft, and long-term immunosuppression.

    - Molecular-genomic studies revealed that EBV-negative PTLD shares many genomic and transcriptomic features with diffuse large B-cell lymphoma in immunocompetent patients, whereas EBV-positive PTLD has fewer genomic abnormalities.
- Although the molecular genetic separation between EBV-positive and EBV-negative PTLD is well defined, EBV status is not prognostic or predictive with respect to treatment response. In a subset of patients, reduction in immunosuppression alone is effective regardless of EBV status.

Risk factors

- EBV donor-recipient mismatch (donor seropositive, recipient seronegative at transplant)
    - EBV donor-recipient mismatch is the most well-established risk factor.
    - There is an 8- to 15-fold increase in PTLD risk and up to 300-fold in the presence of multiple risk factors (such as children or recipients of intestinal transplants).
- Extremes of age (children and advanced age). The increased incidence of PTLD in children is attributed to their pretransplant EBV-naïve status.
- Immunosuppression:
    - Induction with T-cell-depleting antibodies or degree of T-cell immunosuppression (Of note, studies showed no consistent association between PTLD and any individual immunosuppressive agent, suggesting that the overall degree of immunosuppression may play a more important role than any individual agent.)
    - Clinical trials showed an increase in the incidence of PTLD with central nervous system involvement among EBV seronegative transplant recipients who received belatacept. Its use is contraindicated in recipients with pretransplant EBV naïve or unknown EBV serostatus.
- Higher degree of HLA mismatches and individual recipient HLA type (eg, recipient HLA-B38 has been shown to be associated with a 1.48-fold increased risk of diffuse large B-cell lymphoma [DLBCL]. In

contrast, recipient HLA-B58 and HLA-DR13 have been reported to be associated with reduced DLBCL risk.)

- Other risks: White compared with African American race, male gender, pretransplant malignancy, infections with human herpes virus-8 (HHV-8) and simian virus 40, CMV seronegative status at transplant (conflicting data), CMV disease (conflicting data, may be a risk factor), recipient with monoclonal gammopathy of undetermined significance

Time of occurrence after transplant

- PTLD occurs at a median of 18 months posttransplant.
- Most EBV (+) PTLD occur within the first 3 years after transplant.
- Bimodal distribution with time after transplant has been reported: The first peak occurs in the first year posttransplant, and the second peak 5 to 15 years posttransplant.
- Registry studies and the UNOS/OPTN database demonstrated that EBV-negative PTLD generally presents later after transplant (>5 years) and has been suggested to account for the bimodal distribution pattern of PTLD occurrence, with early cases being predominantly EBV positive and late cases being EBV negative. A French registry study suggests that late occurring PTLD (between 8 and 10 years) is less likely to be due to EBV lymphoproliferation and more likely to be a consequence of aging and duration of immunosuppression exposure.
- An increasing number of very late cases occurring more than 20 years has been reported.

Clinical presentation

- Clinical manifestation spectrum spans from incidental asymptomatic findings or constitutional symptoms (eg, fevers, night sweats, malaise, weight loss) to symptomatic organ involvement and spontaneous tumor lysis.
- Localized symptoms may involve the respiratory tract (eg, infection, mass, tonsillitis, or even gingival involvement), GI tract (eg, diarrhea, pain, perforation, bleeding, mass), or central nervous system (eg, headache, seizure, or confusion).

- Extranodal involvement is common and multiple sites are often involved. GI tract involvement has been reported to occur in 20% to 30% of cases, solid graft organs in 10% to 15%, and the central nervous system in 5% to 20%.
- PTLD may also develop in donor organs (allograft PTLD).
  - Generally occurs in the first 2 years after transplant
  - Suggested pathogenic mechanisms: development of lymphoproliferations from donor passenger lymphocytes, chronic antigenic stimulation, EBV proliferation
- Others: symptoms related to allograft dysfunction or compression of surrounding structures
- Clinical presentation of PTLD based on the German multicenter pediatric PTLD registry: Early PTLD (<1 year) development was associated with younger age, extranodal disease, graft organ involvement, and was often of B-cell lymphoma histology and tended to be EBV positive. Burkitt lymphoma and Hodgkin disease were only observed in late PTLD (>1 year) and were more likely to be associated with nodal disease.
- Mortality is greater with PTLD than with lymphomas in the general population.

Treatment

- Treatment strategies include immunosuppression reduction or discontinuation (should be first-line therapy), surgical resection with or without local radiation for localized disease, rituximab (for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone), and chemotherapy. Adoptive immunotherapy using EBV-specific cytotoxic T cells has been reported to be effective in relapsed or refractory PTLD. However, such therapy requires specialized techniques and is not readily available. For PTLD involving the central nervous system, whole-brain radiation is a therapeutic option for those who cannot undergo chemotherapy due to specific contraindications.
- Antiviral therapy: The use of acyclovir and ganciclovir is of unproven benefit because their activity is dependent on intracellular

phosphorylation by virally coded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase.

- mTOR inhibitors: Although sirolimus has antiproliferative effects, there are insufficient data to recommend or refute its use in the treatment of PTLD. While a direct antitumor effect cannot be excluded, it is speculated that the beneficial effect of conversion to sirolimus monotherapy (or sirolimus and prednisone dual therapy) may be due to a reduction in overall immunosuppression.
- Discussion of PTLD treatment modalities is beyond the scope of this chapter. Interested readers are referred to **Appendices A9.7 and A9.8**.

Retransplantation after PTLD

Re-allograft transplant candidates should be disease-free for at least 2 years prior to retransplantation (see **Table 9.3**). Consultation with Hematology/Oncology is recommended.

MALE AND FEMALE FERTILITY

Pregnancy

Considerations prior to conception

Time from transplant: Patient must be at least 1-year posttransplant and on stable immunosuppression prior to conception consideration.

Allograft function

- No acute rejection episodes in the previous year
- SCr of less than 2.0 mg/dL, preferably of less than 1.5 mg/dL (Higher creatinine level increases the risk of allograft loss and maternal and fetal complications.)
- Minimal or no proteinuria/albuminuria (minimal proteinuria defined as <500 mg/24 h)
- Normal kidney allograft ultrasound

Control of comorbidities

- Well-controlled HTN on minimal antihypertensive regimen
- No acute infections that may impact fetal growth and well-being (eg, congenital CMV infection can cause birth defects and/or

developmental delays)

Drug safety in pregnancy

- Drugs that may be used during pregnancy: cyclosporine, tacrolimus, and AZA
- Drugs that should not be used during pregnancy:
  - MPA derivatives (MMF or mycophenolate sodium) due to increased risk of first-trimester pregnancy loss and congenital malformation
  - mTOR inhibitor sirolimus or everolimus has been shown to be associated with increased fetal mortality, decreased fetal weights, and delayed ossification of skeletal structures.
  - Use reliable contraception while on MPA derivatives or mTOR inhibitors and for 3 months after discontinuation.
  - Belatacept: Clinical studies on belatacept use in pregnancy are currently limited. In a case series consisting of 16 pregnancies in 12 recipients, there were 13 live births and 3 miscarriages. No birth defects or fetal deaths were reported in any of the live births. Pregnancy outcomes were reported as comparable to those receiving CNI-based immunosuppression. *FDA pregnancy category:* not assigned
- Breastfeeding and immunosuppressive therapy
  - Cyclosporine, tacrolimus, prednisone, and AZA: may be used during breastfeeding
  - MPA derivatives, mTOR inhibitors, belatacept: long-term safety data lacking

Male Fertility

- Fertility, as assessed by sperm counts, improves in half of patients.
- There is no increased incidence of neonatal malformations in pregnancies fathered by kidney transplant recipients.

MULTIORGAN TRANSPLANTATION

Kidney and Pancreas

Kidney and pancreas transplant options for patients with type 1 diabetes

Simultaneous pancreas-kidney (SPK) transplantation

- Pancreas transplantation performed simultaneously with kidney transplantation from the same deceased donor (most common surgical procedures done)
- Advantage: one surgical intervention and one source of foreign HLA
- Among pancreas recipients, those with an SPK transplantation were found to have the best pancreas graft survival rates.
- Selected patients with ESKD with insulin-dependent type 2 diabetics (ie, body mass index <30 kg/m^2, minimal insulin resistance and worsening glycemic control may be appropriate candidates for SPK. Discussion is beyond the scope of this chapter.

Pancreas after kidney transplantation (PAK)

- Pancreas transplantation performed after successful kidney transplantation from a living or deceased kidney donor
- Advantage: important option for patients with a living donor kidney
- Disadvantage: Intensification of immunosuppression (particularly in the early postoperative period) after pancreas transplantation can adversely impact kidney allograft function due to CNI toxicity.
- Must have adequate baseline renal function to undergo PAK

Pancreas transplantation alone (PTA)

- Least common surgical procedures performed
- Therapeutic option for patients with diabetes with good native kidney function who have brittle diabetes particularly those with hypoglycemic unawareness
- Main risks: surgical procedure and long-term effects of immunosuppression
- In recent years, the number of PAK or PTA performed in the United States has decreased, thought to be due in part to advances in diabetes technology: The use of continuous glucose monitoring (CGM) and automated insulin delivery systems have been shown to decrease both hypo- and hyperglycemic episodes and improve health-related quality of life in type 1 diabetics.

Kidney and Liver

Liver candidate with established ESKD (or eGFR ≤20 mL/min)

Simultaneous liver-kidney transplantation (SLKT) is a well-established therapeutic option for suitable liver transplant candidates with simultaneous end-stage kidney failure (or eGFR ≤20 mL/min).

Liver transplant candidate with CKD or AKI

- The UNOS/OPTN eligibility criteria for SLKT in liver transplant candidates with CKD or sustained AKI is summarized in **Table 9.31**.
- Safety net

Table 9.31 UNOS/OPTN eligibility criteria for simultaneous dual organ transplantation (liver-kidney, heart-kidney, or lung-kidney)

Liver, heart, or lung transplant candidates with CKD	Liver, heart, or lung transplant candidates with sustained acute kidney injury (sustained AKI)	Liver transplant candidates with confirmed diagnosis of metabolic disease (not applicable for heart or lung transplant candidates)
Preexisting CKD defined as measured or calculated CrCl or GFR of ≤60 mL/min for more than 90 consecutive days prior to listing	Sustained AKI defined as AKI present for at least 6 consecutive weeks (must be documented in patient's medical records every 7 d).	
Dual organ eligibility CKD defined above *and* at least one of the following criteria must be present: 1. Patient has begun regular dialysis as a patient with end-stage kidney disease. 2. Most recent measured or calculated CrCl or GFR ≤30 mL/min. 3. On a date after registration on the	**Dual organ eligibility** Sustained AKI defined above *and* at least one of the following criteria must be present: 1. AKI requiring acute dialysis *or* 2. Measured or calculated CrCl or GFR ≤25 mL/min *or* 3. Any combination of no. 1 and no. 2	**SLKT eligibility** At least one of the following diagnoses must be present: 1. Hyperoxaluria 2. Atypical hemolytic uremic syndrome (aHUS) from mutations in factor H and possibly factor I 3. Familial nonneuropathic systemic amyloid 4. Methylmalonic aciduria

Liver, heart, or lung transplant candidates with CKD	Liver, heart, or lung transplant candidates with sustained acute kidney injury (sustained AKI)	Liver transplant candidates with confirmed diagnosis of metabolic disease (not applicable for heart or lung transplant candidates)
kidney waiting list, measured or calculated CrCl or GFR ≤30 mL/min.		

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CrCl, creatinine clearance; GFR, glomerular filtration rate; SLKT, simultaneous liver-kidney transplantation; UNOS/OPTN, United Network for Organ Sharing/Organ Procurement Transplantation Network.

From United Network for Organ Sharing. New data fields available June 29 to prepare for simultaneous heart-kidney and lung-kidney allocation. Accessed July 15, 2024. https://unos.org/news/policy-changes/new-data-fields-available-june-29-shk-sluk/

- Recipients of liver-alone transplant whose renal function does not recover (eGFR remains ≤20 mL/min or dialysis dependent) between 60 and 365 days after a successful liver transplant are given a degree of *"increased priority"* in being offered a deceased donor kidney.
- The implementation of the safety net may relieve the clinician's pressure to perform SLKT when a liver-alone transplant may suffice.

Kidney and Heart/Kidney and Lung

Simultaneous heart-kidney transplantation and simultaneous lung-kidney transplant medical eligibility criteria

- Eligibility criteria for simultaneous heart-kidney and simultaneous lung-kidney transplantation in patients with CKD or sustained AKI: same criteria as simultaneous liver-kidney allocation for liver transplant candidates with CKD and sustained AKI as outlined in **Table 9.31**
- Safety net
  - Similar to liver transplant recipients with nonrecovery of renal function after liver transplantation, the safety net policy ensures

access to kidneys for heart and lung transplant recipients with nonrecovery of renal function after heart or lung transplantation, respectively.

- Nonrecovery of renal function is defined as eGFR 20 mL/min or less or dialysis dependent between 60 and 365 days after heart or lung transplantation.
- Safety net policies for kidney-after-heart or kidney-after-lung transplantation are similar to the safety net provision already in effect for kidney-after-liver allocation.

CHAPTER 10

Pharmacology

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PHARMACOKINETICS

Key Concepts

Bioavailability, volume of distribution, plasma protein binding, loading dose, plasma clearance (Cl), drug half-life

Bioavailability

Bioavailability is the percentage or portion of an administered drug that actually reaches systemic circulation.
Intravenous (IV) route: Bioavailability is 100%.
Nonintravenous route: Bioavailability depends on:

- Ease of absorption (ie, through gut, skin, or mucosal membrane)
- First-pass metabolism (ie, hepatic metabolism prior to release into systemic circulation)

Factors that can alter bioavailability in renal patients

- Increased salivary urea in uremia increases salivary pH, which reduces absorption of drugs that are better absorbed in acidic pH.
- Nausea/vomiting can cause loss of oral drugs.
- Gastroparesis/reduced peristalsis slow drug absorption and delay attainment of plasma peak concentration.
- The use of antacids and proton pump inhibitors (PPIs) can increase stomach pH, which reduces absorption of drugs that are

better absorbed in acidic pH (eg, iron, mycophenolate mofetil [MMF] [CellCept] but not mycophenolate sodium [Myfortic]).
- Phosphate binders can form nonabsorbable complexes with some drugs (eg, quinolones).
- Bowel wall edema (eg, nephrosis) reduces gut absorption.

Volume of distribution (V_d)

- The total amount of drug in the body, expressed as an imaginary volume with a uniform drug plasma concentration:
  - V_d is large for drugs with a high degree of lipid solubility, compartmentalization, and low plasma protein binding.
  - Volume of distribution (V_d) = Total amount of drug in the body ÷ Plasma concentration of drug
  - V_d is traditionally expressed as L/kg of ideal body weight.

Plasma protein binding

- Plasma protein binding is a key determinant of V_d (**Figure 10.1**).

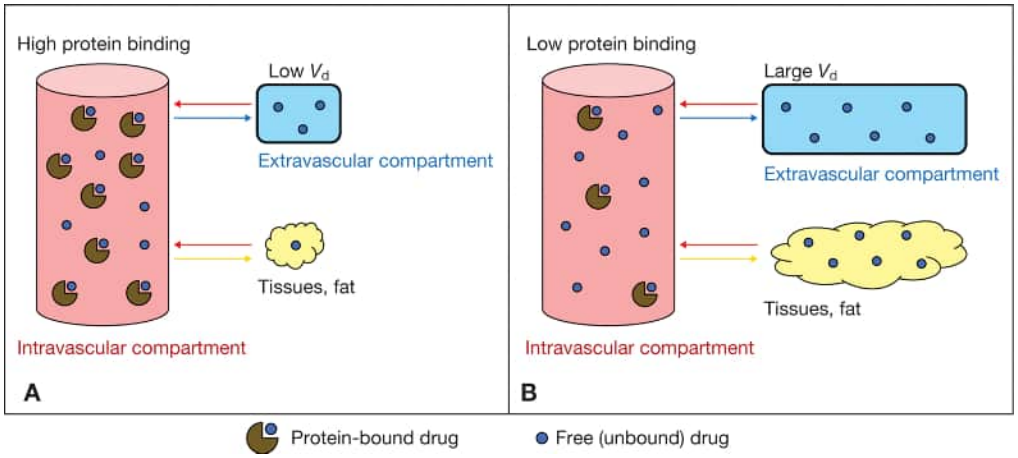

FIGURE 10.1 Volume of distribution (V_d). A. V_d is low for drugs with high plasma protein binding and high water solubility. B. V_d is large for drugs with low plasma protein binding, high lipid solubility, and compartmentalization.

- Drugs that are highly protein bound stay in the vascular compartment and have a limited V_d.
- V_d is low for drugs with high water solubility and high plasma protein binding.

Major drug-binding proteins include albumin and α1-acid glycoproteins

- Organic acids generally bind to albumin.
- Organic bases generally bind to glycoproteins. Increased synthesis of α1-acid glycoproteins may occur in inflammatory states and may alter free drug levels.

Factors that alter plasma protein binding in **renal patients**

- Reduced serum proteins due to renal loss (eg, nephrotic syndrome), malnutrition, and/or reduced synthesis. In patients with albuminuria, protein-bound drug may be lost in the urine.
- Competitive binding of uremic toxins to plasma proteins displaces protein-bound drugs into plasma, resulting in increased free (unbound) drug concentrations.
- Organic acids that accumulate in renal failure compete with acidic drugs for protein binding. Therefore, a larger fraction of acidic drugs will exist in the unbound active state (eg, salicylates, warfarin, sulfonamides, phenytoin).
- Alteration in blood pH

Loading dose

$$\text{Loading dose} = \frac{(\text{Desired peak drug concentration} \times V_d \times \text{Ideal body weight})}{\text{Bioavailability}}$$

where bioavailability = 1 for IV drug infusion.

- Loading dose is directly proportional to V_d.
- In the absence of a loading dose, maintenance doses alone will not achieve steady-state level until five drug half-lives later. Thus, for some drugs, a loading dose is given to reduce the time to

steady state when it is critical to rapidly achieve therapeutic concentrations (eg, administration of antibiotics in the setting of sepsis or septic shock).

Factors that can alter V_d in renal patients

- Increased V_d: edema, ascites/effusions, adsorption onto apparatus (dialysis filters, extracorporeal membrane oxygenation [ECMO] circuits), volume expansion due to extracorporeal machinery (an extra 2,000-2,500 mL)
- Reduced V_d: increased age, muscle wasting, amputations, loss of body fat, volume depletion
- Effect of reduced plasma protein binding on V_d: Predicting the effect of reduced plasma protein binding on the volume of distribution may be difficult. Although more free drug is available for redistribution into other extravascular compartments, which can result in increased V_d, more is also available for metabolism or renal excretion. The latter can result in reduced V_d.

NOTE

A patient's actual V_d of drug A may be calculated as V_d = Loading dose of A ÷ (post[A] – pre[A]), where pre[A] and post[A] are, respectively, plasma concentrations of drug A pre- and postdrug loading. When a patient's actual V_d of a drug is greater than that published in the drug insert, a higher dose may be needed. Similarly, if the patient's actual V_d is smaller than that published, dose reduction is necessary.

Plasma Cl

- Most drugs are cleared/metabolized by the liver and/or kidneys. Plasma Cl is the sum of Cl of a drug by both renal and nonrenal routes.
- There is evidence that renal impairment may also reduce nonrenal (ie, hepatic) metabolism of drugs, presumably via an increase in a circulating inhibitor of hepatic metabolic pathways (cytochrome P450). This factor is thought to be dialyzable.
- Drug Cl determines *maintenance dose.*

- Dose adjustment based on altered drug Cl in a patient with kidney failure:

Example 1: A drug is 100% renally excreted. Normal maintenance dose is 100 mg. If kidney function is now 30% of normal, what should be the new maintenance dose?
Maintenance dose should be reduced to 30% of the normal dose, 30 mg.
Example 2: A drug is 40% cleared by liver and 60% by kidneys. Normal maintenance dose is 100 mg. If kidney function is now 40% of normal and assuming liver Cl is preserved, what should be the new maintenance dose?
Cl of the drug is still 40% by liver, but now, Cl by kidneys is only 40% of 60%, which is 24%. Total drug Cl would now be 40% by liver plus 24% by kidneys, or 64% total Cl. Maintenance dose should be reduced to 64% of the normal dose, 64 mg.

Half-life (*t*½)

- A drug *t*½ is the time needed for the plasma level of the drug to decrease by 50%.
- Generally, for an oral drug, four to five half-life duration are needed to reach steady state. Example: For a drug with *t*½ of 12 hours, it takes up to 5 × 12 hours = 60 hours (2½ days) to reach steady state. If an immediate therapeutic level is needed, a loading dose must be given.
- Half-life determines *dosing frequency*.

NOTE

The pharmacokinetic t½ of a drug is not the same as its pharmacologic "effect" half-life. A drug may be cleared from the blood, but its pharmacologic effect (pharmacodynamics) may still persist (eg, aminoglycosides [AG], glucocorticoids [GCs], immunosuppressive agents).

Therapeutic Drug Monitoring

- Therapeutic drug monitoring can be very valuable in guiding dosage adjustment for drugs with wide inter- and intrapatient variation in pharmacokinetics or for drugs with a narrow therapeutic index or concentration-dependent activity (eg, AG, digoxin, lithium, anticonvulsants, and immunosuppressive medications).
- The pharmacokinetic and pharmacodynamic (pharmacologic effect) properties of a drug determine how therapeutic drug monitoring is performed (peak concentrations vs trough concentrations).

Renal Handling of Drugs

Renal drug Cl

- Renal drug Cl = total amount of drug in urine ÷ plasma concentration of drug = UV/P of drug (and its metabolites if applicable)

where U = urine concentration of drug, V = urine volume, and P = plasma concentration of drug.

- Renal drug Cl is dependent on the drug characteristics (molecular size, charge, protein binding), glomerular filtration rate (GFR), tubular secretion and reabsorption, and renal epithelial cell metabolism.
- Drug $t½$ is directly proportional to V_d and inversely proportional to renal drug Cl. $t½ = 0.693 \times V_d/\text{Cl}$, where 0.693 is the natural logarithm of 2 for half-life decay.

Drug adjustment in patients with renal impairment

- Dose reduction in patients with chronic kidney disease (CKD) is generally indicated when 30% or more of a drug or its active metabolite is normally cleared by the kidneys. Of interest, when a drug is cleared by 30% or more with dialysis, the drug is considered "dialyzable."

- Estimation of kidney function for dose adjustment is traditionally done with the Cockcroft-Gault equation. Given multiple different equations that can be used to estimate kidney function, it is advisable to read drug inserts provided by the pharmaceutical company regarding their method of estimating kidney function in determining renal dosing.
- Acute and severe kidney injury: Assume less than 10% kidney function and dose accordingly.
- Rapidly improving kidney function: Dose drug as if patient had normal kidney function.

Three methods for maintenance dose adjustments in patients with renal impairment

Decrease dosage: This is the preferred method when maintaining constant drug level is more critical than achieving high peak levels for therapeutic effect (eg, anticonvulsants, antiarrhythmics). Modified maintenance dose for renal impairment may be calculated as the (ratio of patient's creatinine clearance [CrCl] to normal CrCl) × standard maintenance dose.

Example: A patient with CrCl 69 mL/min (normal CrCl 120 mL/min) on a standard maintenance drug dose of 100 mg q8h. Modified dose = (69/120) × 100 = 58 or approximately 60 mg q8h.

Reduced drug administration frequency: Preferred method if peak level is critical for therapeutic effect (eg, antimicrobials such as AG). Modified drug administration frequency for renal impairment may be calculated as the (ratio of normal CrCl to patient's CrCl) × current frequency. The modified frequency for the above example would be (120/69) × 8 hours = 14 hours. For simplicity, the drug can be given as 100 mg q12h.

Combination of above: Preferred method for drugs with narrow therapeutic index (eg, digoxin). For the same patient above, the drug can be given as 80 mg q10h.

NOTE

Dose adjustment in patients with CKD or end-stage kidney disease (ESKD) may also be needed because the pharmacologic effects of some drugs may be exaggerated due to increased target organ sensitivity (eg, exaggerated sedation with narcotics in patients with ESKD despite appropriate dose reduction).

Principles of Dialytic Drug Removal

- Dialysis drug Cl may occur via both diffusion and convection.
- Drug Cl by dialysis is considered clinically significant, that is, "dialyzable," if drug Cl is increased by 30% or more with dialysis.
- Whenever feasible, close therapeutic drug monitoring is recommended.

Drug Cl is dependent on characteristics of the drug and the dialysis procedure

Drug characteristics: molecular size (<500 Da for hemodialysis [HD], up to 5,000 Da for continuous kidney replacement therapy [CKRT]), water solubility, protein binding, V_d, degree of compartmentalization of drug, plasma Cl

Dialysis characteristics: membrane pore size, blood and dialysate flow rates, dialysis frequency and duration, ultrafiltration rate, replacement solution location in CKRT (predialysis vs postdialysis)

Special considerations for different modes of dialysis

Hemodialysis (HD)

- Drug Cl is dependent on dialysis membrane characteristics, blood and dialysis flow rates, dialysis frequency and duration.
- Drug Cl = drug extraction ratio × blood flow, where extraction ratio = (predialysis concentration − postdialysis concentration) ÷ predialysis concentration
- "High-efficiency," "high-flux," and "high-permeability" dialysis membranes can lead to significantly higher drug Cl, particularly for highly water-soluble drug. Example: Vancomycin Cl is significantly increased with high-flux membranes.

Peritoneal dialysis (PD)

- Protein-bound drugs may be better cleared with PD compared with HD due to larger peritoneal membrane pore size.
- Drug Cl by PD is typically approximated at 10 mL/min.
- Drug Cl by PD may increase with the following:
  - Peritonitis due to increased blood flow
  - Increase number of daily exchanges

CKRT: hemodiafiltration

- Drug is removed by both diffusion (dialysis) and convection (hemofiltration).
- Drug Cl by convection = sieving coefficient of drug × ultrafiltration rate, where sieving coefficient = drug concentration in ultrafiltrate ÷ drug concentration in arterial line (prefilter blood)
- A sieving coefficient of 1 implies that a drug is freely filterable across the dialysis membrane, whereas a sieving coefficient much less than 1 implies poor drug dialyzability. Dialysis membrane pore size is the key determinant of sieving coefficient. Sieving coefficients are published in the literature for various drugs.
- Effect of fluid replacement location:
  - Prefilter replacement fluid increases ultrafiltration rates, hence higher proportion of drug removal by convection.
  - Postfilter replacement fluid increases the proportion of drug that is removed by diffusion.

NOTE

- For CKRT dose of 25 to 35 mL/kg/h, antibiotics can be easily underdosed. Maintenance dosing on the higher rather than lower side is recommended. Loading dose is unchanged.
- Renal dose adjustment for CKRT is based on CKRT drug Cl, estimated as CKRT Cl = unbound drug fraction × effluent rate.

Plasmapheresis

- Literature on drug removal with plasmapheresis is lacking.
- Plasmapheresis may significantly remove drugs with high plasma protein binding and/or low V_d.
- Intravenous immunoglobulin (a.k.a. IVIG), rituximab, and antithymocyte globulin (ATG) are removed by plasmapheresis. Although the extent of drug removal by such procedure is unknown, as much as a 50% dose loss during plasmapheresis has been described. These agents should be administered immediately after plasmapheresis if possible.

DRUG SELECTION AND DOSE ADJUSTMENT IN KIDNEY DISEASE

Antimicrobials Agents

Many agents are small (<500 Da), water soluble, not highly protein bound, and appear unchanged in the urine. Dosage reduction is thus usually necessary in patients with CKD and dialysis dependency.

Aminoglycosides (AG)

- Bactericidal activity of AG is dependent on the initial rapid intracellular accumulation, followed by significant tissue release postantibiotic administration. The latter is termed "postantibiotic effect." Drugs with "postantibiotic effect" depend on the loading dose but require less frequent dosing.
- AG are mostly excreted unaltered by glomerular filtration and to a much lesser extent by tubular secretion—tubular reabsorption can lead to high renal cortical tissue concentrations even in advanced renal impairment.

Dosing of AG

- In general, daily dosing or even q36h to q48h dosing of AG is thought to minimize nephrotoxicity in patients with GFR less than 60 mL/min.

- Dosing for all AG is based on ideal body weight and adjusted body weight for patients who are obese. Serum levels should be measured to ensure therapeutic levels and avoidance of toxicity.
- In HD, predialysis dosing of AG allows for higher maximal concentration and theoretically better efficacy. Postdialysis dosing of half dose has also been suggested, but potential for higher toxicity must be noted.
- AG drug removal is thought to be greatest with continuous venovenous hemodiafiltration (CVVHDF) (significant solute removal by both diffusion and convection), followed by continuous venovenous hemofiltration (CVVH) (significant solute removal by convection) and intermittent HD (predominantly diffusion).
- In peritonitis, AG should be given intraperitoneally.

AG nephrotoxicity and ototoxicity

- AG can cause nephrotoxicity and ototoxicity due to intracellular accumulation and associated injury to lysosomes, Golgi apparatus, mitochondria, and endoplasmic reticulum in proximal tubular cells and inner ear hair cells, respectively.
- AG nephrotoxicity is typically evidenced by a rise in serum creatinine (SCr) within 7 to 10 days of exposure.

Nephrotoxicity risks: older age, underlying CKD, diuretics, concurrent use of nephrotoxic agents or IV radiocontrast agents, hypokalemia, hypovolemia

Electron microscopy reveals "myeloid bodies" in proximal tubular cells. Myeloid bodies are thought to arise from drug trapping, followed by a gradual accumulation of drug-phospholipid complexes within the internal lysosomal membranes. The increase in undigested materials interferes with normal membrane activity and results in the accumulation of concentric multilamellar lipid layers known as myeloid bodies, which may have similar appearance as those seen in Fabry disease (see **Chapter 7: Glomerular and Vascular Disorders**).

NOTE

AG and tetracycline can lead to proximal renal tubular acidosis (RTA) and/or Fanconi syndrome. In addition, their ability to bind the CaSR can lead to Bartter-like syndrome where patients develop metabolic alkalosis and urinary K^+, Ca^{2+}, Mg^{2+}, and Na^+ wasting.

Glycopeptides (vancomycin and teicoplanin)

- Both are predominantly excreted by the kidneys. Teicoplanin is not available in the United States.
- When given IV, both agents are nephrotoxic and ototoxic, but teicoplanin is less nephrotoxic.
- Nephrotoxicity is thought to involve oxidative stress. Use of vitamin E and *N*-acetylcysteine has been suggested to ameliorate vancomycin-induced nephrotoxicity.
- Nephrotoxic risks include underlying kidney injury, concurrent use of nephrotoxic drugs, prolonged therapy, and high plasma levels.
- Dialysis vancomycin dosing of 1 g can maintain plasma level above minimum inhibitory concentration (>15 µg/mL) for 3 to 5 days. Of note, trough levels greater than 15 µg/mL are associated with greater nephrotoxicity. Random level monitoring may be used to determine the timing of subsequent doses among patients with KRT or advanced CKD not on scheduled dosing.

β-Lactams

- Most (penicillins, cephalosporins, carbapenems, monobactams) require dose reduction in CKD. β-Lactams are commonly combined with β-lactamase inhibitors (eg, clavulanate, sulbactam, tazobactam, avibactam) to minimize antibiotic resistance and improve activity spectrum. Dose adjustment for combination drugs must consider the different metabolism rates of both agents. Whereas rates of metabolism of both agents in ampicillin/sulbactam and piperacillin/tazobactam are similar, clavulanate metabolism is much faster than that for ticarcillin in the ticarcillin/clavulanate combination.

- Unlike AG, most β-lactams have a short half-life and no postantibiotic effect. Dose reduction is generally preferred over frequency reduction.
- Central nervous system (CNS) toxicity leading to a lower seizure threshold is not uncommon with β-lactams (eg, penicillins, imipenem) when used in high unadjusted dose in patients with advanced CKD.

NOTE

Penicillin can lead to either hypokalemia or hyperkalemia depending on its formulation.

Hypokalemia: This is due to excess K^+ excretion that occurs with the high content of nonabsorbable anions in the penicillin formulation.

Hyperkalemia: This is due to the high content of K^+ in some formulations in association with inadequate kidney K^+ excretion.

Sulfonamides and trimethoprim

- Sulfonamides are typically combined with trimethoprim.
  - Both are renally excreted. However, alkaline urine enhances the excretion of sulfamethoxazole, whereas acidic urine promotes trimethoprim excretion.
  - Both accumulate in renal impairment, and dosage adjustment is recommended.
- Sulfonamides are excreted following acetylation. Acetylated sulfonamides may crystallize in tubular lumen and cause kidney injury, particularly with cumulative dose greater than 84 g. Crystallization is enhanced in acidic urine. Good hydration and alkalinization may be both preventive and therapeutic.
- Sulfonamides may also cause tubulointerstitial nephritis.
- Trimethoprim may inhibit tubular secretion of creatinine and may cause a rise in SCr without actually causing kidney injury.
- Trimethoprim may block the epithelial sodium channel (ENaC) and cause both hyperkalemia and metabolic acidosis.

Rifamycins

- Rifamycins are predominantly hepatically metabolized. No renal adjustment is needed.
- Rifamycins may cause orange reddish discoloration of body fluids, such as urine, effusions, and PD fluids.
- Rifampin may cause various renal lesions, including acute tubular necrosis (ATN), acute interstitial nephritis (AIN), light-chain proteinuria, and even rapidly progressive glomerulonephritis (RPGN). The type of lesion appears to be associated with how the drug is given.
  - Intermittent use (eg, noncompliant patient) is associated with ATN, with or without interstitial infiltrations, hemolysis, and thrombocytopenia.
  - Continuous use is associated with light-chain proteinuria and RPGN.
- Rifampin is a potent CYP3A4 inducer and can cause subtherapeutic concentrations and treatment failure of many drugs, including GC, calcineurin inhibitors (CNIs) (cyclosporine [CsA], tacrolimus [Tac]), mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), and statins. Dose increase of affected drugs is generally required.

Fluoroquinolones

- Ciprofloxacin and norfloxacin are significantly renally excreted and must be dose reduced for GFR below 30 mL/min.
- Moxifloxacin is only 20% renally excreted and does not require dose adjustment.
- Quinolones may cause nonspecific CNS symptoms, including headaches, dizziness, restlessness, tremors, and kidney injury from interstitial nephritis and/or crystalluria.
- Quinolone absorption is reduced with metal-containing compounds and phosphate binders.

Nitrofurantoins

There are concerns for toxic accumulation in patients with advanced CKD and potential for pulmonary and hepatic toxicity and peripheral neuropathy. The U.S. Food and Drug Administration (FDA)-approved labeling states that the use of nitrofurantoin is contraindicated in patients with a CrCl less than 60 mL/min. Nonetheless, data are lacking to support this recommendation. Retrospective studies have shown that short-term nitrofurantoin use is effective and generally well tolerated in patients with a CrCl of 30 mL/min or more, although higher adverse events have been noted in patients with renal impairment.

Other antibiotics

Tetracyclines

- Tetracycline depends more on renal excretion than doxycycline or minocycline. It should be avoided in patients with renal impairment because it has a catabolic effect, thus potentially leading to uremia, hyperphosphatemia, and metabolic acidosis. It may also aggravate preexisting kidney injury.
- Outdated tetracycline may result in renal tubular damage and Fanconi-like syndrome.
- Doxycycline, tigecycline, and standard dose minocycline: No dose adjustment is needed. For CrCl less than 80 mL/min, the minocycline maximum dose is 200 mg/d.

Linezolid

- No dose adjustment is needed.
- Linezolid and tetracyclines can cause type B lactic acidosis. See **Chapter 2: Acid-Base and Potassium Disorders**.

Metronidazole

- No specific dose adjustment is recommended for patients with renal impairment.
- Metronidazole is extensively removed by dialysis. Administer postdialysis on dialysis days.

- CKRT: dose as for normal renal function

Macrolides

- Azithromycin, clarithromycin, roxithromycin (hepatically cleared): No dose adjustment is needed.
- Erythromycin (renally cleared): Dose reduction is required.

Antifungals

Amphotericin

Acute kidney injury (AKI)

- AKI typically occurs after 2 weeks of therapy and is associated with the cumulative dose received. Lipid formulations can allow additional doses to be given by delaying the onset of nephrotoxicity.
- Risks: older age, underlying CKD, hypovolemia, hypokalemia

Electrolyte and acid-base disturbances

- Distal RTA, renal magnesium and potassium wasting
- Liposomal or lipid-based formulations confer lower AKI and electrolyte disturbances and are preferred in patients with any degree of residual kidney function. Acute allergic reaction may be seen with lipid-based formulations. Of interest, some chemistry analyzers can erroneously read phosphorus from phospholipid-based formulations of amphotericin as serum phosphorus, leading to pseudohyperphosphatemia.

Other notable adverse effects: nephrogenic diabetes insipidus, arteriolar vasoconstriction (afferent greater than efferent arterioles), anemia with or without thrombocytopenia presumably due to high inorganic content in liposomal formulations, and possibly measurement interference/error

Management of **IV amphotericin-B–induced nephrotoxicity**

- Routine preventive measures: normal saline, use of lipid formulations of amphotericin-B, reduce administration frequency if possible. Of note, lipid formulations of amphotericin are not recommended for the treatment of fungal urinary tract infections

(UTIs). The addition of the lipid component may reduce its therapeutic effectiveness by interfering with the drug's ability to achieve adequate levels in the urinary tract.

- Other suggested measures:
  - Continuous infusion may be less nephrotoxic compared with intermittent large dosing.
  - Consider the use of low-dose calcium channel blockers (eg, diltiazem) to reduce renal vasoconstriction if safely tolerated.
- Amphotericin is highly protein bound (~90%-95%) with a large V_d and is thus not easily dialyzable. The large V_d is likely due to large tissue uptake.

Azoles

- With the exception of fluconazole, most agents (ketoconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are metabolized by the liver and do not require dose reduction.
- Most azoles are potent inhibitors of CYP3A4 that are involved in the metabolism of many drugs including CNIs (CsA, Tac), mTOR inhibitors (sirolimus, everolimus), and statins.
- Most azoles are also potent inhibitors of *P-glycoproteins that are involved in the metabolism and absorption of many drugs, including Tac, mTOR inhibitors (sirolimus, everolimus), and statins.
- Voriconazole, ketoconazole, itraconazole, and posaconazole are strong inhibitors of CYP3A4.
- Fluconazole and isavuconazole are moderate CYP3A4 inhibitors.
- Dose reduction of the affected drug (CNIs, mTOR inhibitors, statins) is generally required.

NOTE

*P-glycoproteins normally serve to secrete various drugs into the gastrointestinal (GI) tract and renal tubular lumen or increase exposure of drugs to CYP enzymes for metabolism, thus effectively reduces blood levels of the affected drugs.

Diarrhea/enterocolitis may lead to reduced intestinal P-glycoprotein activity and significantly increase blood levels of drugs that are substrates of P-glycoproteins. It is well observed that patients receiving Tac, a P-glycoprotein substrate, can present with toxic levels during episodes of diarrhea or enterocolitis.

Fluconazole is significantly excreted in the urine and is preferred for the treatment of UTIs. After an adequate loading dose, maintenance dose should be reduced in moderate-to-severe renal impairment. Fifty percent dose reduction is necessary for GFR less than 60 mL/min. Fluconazole is dialyzable, and the dose should be given after dialysis.

Itraconazole, voriconazole, and posaconazole are mixed with cyclodextrin in IV formulations. Accumulation of cyclodextrin in renal patients can lead to increased SCr and CNS toxicity (eg, agitation, myoclonus, visual and auditory hallucinations, colored or flashing light). IV formulations should be avoided for GFR less than 50 mL/min. Unlike fluconazole, itraconazole, voriconazole, and posaconazole are not dialyzable.

Flucytosine is predominantly excreted in the urine and requires dose adjustment for patients with CKD. Flucytosine has a high rate of fungal resistance and is typically not used as a sole agent, but in combination with amphotericin for severe fungal infections.

Echinocandins (caspofungin, micafungin, anidulafungin)

- Echinocandins are inhibitors of the synthesis of β-D-glucan, a fungal cell wall component. These agents are effective against *Candida* species and azole-resistant *Aspergillus*.
- No dose adjustment is necessary in patients with renal impairment, including those receiving HD or CKRT.
- Unlike azoles, echinocandins typically do not affect CNI levels. However, caspofungin has been shown to reduce Tac levels.

Terbinafine

- Agent used to treat onychomycosis, is metabolized by CYP3A4 and 70% renally excreted
- Plasma Cl is reduced by 50% in patients with CrCl less than 50 mL/min.
- There is no safety data for terbinafine in CKD: 50% dose reduction is suggested in moderate-to-severe renal impairment.

Topical azoles including clotrimazole, econazole, ketoconazole, miconazole, bifonazole, and tinidazole are minimally absorbed and have no drug interaction.

Other antifungals

- Topical and oral nystatin are minimally absorbed. Their use in patients with renal impairment is safe.
- Griseofulvin: No dose adjustment is needed.

Antiviral Agents

Acyclovir and its prodrug valacyclovir, famciclovir

- Renally excreted and may crystallize in tubules leading to obstructive uropathy and AKI, especially when given via rapid infusion. Slow IV infusion over 1 to 2 hours and hydration are critical when given in high dose.
- Associated with leukopenia, neurotoxicity
- Dose reduction based on renal function is necessary.
- Approximately 60% dialyzable. Administer postdialysis on dialysis days.

Ganciclovir and its prodrug valganciclovir

- Renally excreted
- Accumulation may lead to severe bone marrow toxicity.
- Dose reduction based on renal function is necessary.
- Freely dialyzable; should be given after dialysis

Hepatitis B–specific treatments

Lamivudine (3TC), telbivudine, adefovir, tenofovir, and entecavir are extensively renally excreted. Dose adjustment for CrCl less than 50 mL/min is recommended.

3TC is not dialyzable, whereas entecavir and telbivudine are and should be administered postdialysis. Prolonged use of 3TC is associated with drug resistance, and it has been replaced by entecavir and tenofovir.

Entecavir does not induce drug resistance unless the patient has had prior therapy with 3TC or related drugs.

Tenofovir does not induce drug resistance, irrespective of prior treatment. It can cause Fanconi syndrome, proximal tubular cell dysfunction, and AKI.

Tenofovir alafenamide (Vemlidy) is a prodrug of tenofovir with significantly less renal and bone toxicity (less decline in bone mineral density) compared with tenofovir disoproxil fumarate (TDF) (Viread). FDA approved for use in patients with mild-to-moderate renal impairment (CrCl ≥30 mL/min); dialyzable, should be administered postdialysis.

Hepatitis C–specific treatments (Hepatitis C is discussed in Chapter 7: Glomerular and Vascular Disorders)

Ribavirin and its metabolites are renally excreted. Its use should be avoided in patients with CrCl less than 50 mL/min. Ribavirin is associated with hemolytic anemia, thrombotic thrombocytopenic purpura, and red cell aplasia.

Pegylated interferons (INF) α-2a and α-2b require dose adjustment for CrCl less than 50 mL/min. INFs can upregulate cell surface expression of human leukocyte antigen (HLA) class II, leading to acute allograft rejection. However, with the advent of direct-acting antiviral (DAA) agents, INF-based therapy has become obsolete.

Direct-acting antiviral agents

- Sofosbuvir/velpatasvir: No dose adjustment is required for any degree of renal or hepatic impairment.

- Glecaprevir/pibrentasvir: Renal dose adjustment is not required. Its use is not recommended in patients with decompensated cirrhosis because of increased drug levels and risk of worsening liver function or failure.
- Elbasvir/grazoprevir: Renal dose adjustment is not required. Use is contraindicated in patients with Child-Pugh class B or C cirrhosis.
- Ledipasvir/sofosbuvir: No dose adjustment is required for renal or hepatic impairment.

Anti-influenzal agents (neuraminidase inhibitors)

- Oseltamivir (Tamiflu) and peramivir (Rapivab) are renally excreted and require dose reduction for reduced GFR. Oseltamivir should be given at half dose (30 mg) with CrCl less than 60 mL/min, and at half dose once daily with CrCl less than 30 mL/min.
- Zanamivir (Relenza) is extensively renally excreted after IV doses. However, its bioavailability from inhaled doses is only approximately 2%, which does not require dose reduction. Zanamivir oral inhalation has been removed from the U.S. market.

Antiretroviral Agents

Table 10.1 summarizes the mechanisms of action and important notes relating to the kidneys for commonly used antiretroviral agents.

Table 10.1 HIV drugs and the kidney

	Mechanism of action	Common drugs	Dose adjustments	Renal effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	NRTI incorporates itself into the DNA during reverse transcription of the viral	Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC)	Yes	Fanconi syndrome has been reported with the use of ABC, ddI, 3TC, and

	Mechanism of action	Common drugs	Dose adjustments	Renal effects
	genome and effectively terminates DNA polymerization.	Lamivudine (3TC) Tenofovir (TDF) Zidovudine (AZT, ZDV)		both formulations of tenofovir (tenofovir disoproxil fumarate [TDF] and tenofovir alafenamide). nDI may occur with ABC, ddI, and TDF. Type B lactic acidosis may occur with all NRTIs.
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	NNRTIs are small hydrophobic chemical compounds that bind to a pocket near the active site of HIV reverse transcriptase, thereby reducing its ability to optimally catalyze DNA polymerization.	Efavirenz (EFV) Etravirine (ETR) Nevirapine (NVP) Rilpivirine (RPV)	Yes	
Protease inhibitors (PIs)	PIs bind to and inhibit the HIV aspartyl protease, an enzyme involved in the processing of viral proteins. This inhibits	Atazanavir (ATV) Darunavir (DRV) Lopinavir (LPV) Ritonavir (RTV)	No *SQV use is not recommended in severe CKD.*	PIs may crystallize in renal tubules and cause urolithiasis. *IDV has been largely replaced by ATV and DRV.*

	Mechanism of action	Common drugs	Dose adjustments	Renal effects
	viral maturation, thus the formation of a functional virion.	*Indinavir (*IDV*)* *Saquinavir (*SQV*)*		*SQV is also associated with hypocalcemia and lactic acidosis.*
Integrase inhibitors	Integrase inhibitors block the integration of HIV DNA into human DNA by the HIV integrase enzyme.	Raltegravir (RAL) Elvitegravir (EVG) Dolutegravir (DTG)	No	Elvitegravir is metabolized by CYP3A4 and may have potential CNI-drug-drug interaction. Dolutegravir may increase SCr via inhibition of renal tubular secretion of Cr.
Fusion inhibitor	Fusion inhibitors inhibit the fusion of the HIV envelope with human cell membranes.	Enfuvirtide (ENF, T-20)	No	Enfuvirtide may be associated with MPGN.
CCR5 inhibitor	CCR5 inhibitor binds to the external portion of the transmembrane receptor CCR5 that serves as the co-receptor for virus entry.	Maraviroc (MVC)	No Avoid use in patients requiring dialysis or with CrCl <30 mL/min.	

	Mechanism of action	Common drugs	Dose adjustments	Renal effects
Pharmacokinetic (PK) enhancer	PK enhancers are inhibitors of cytochrome P450 (CYP) 3A enzymes that act as a drug-level booster for the protease inhibitors atazanavir and darunavir.	Cobicistat (COBI)	No	Cobicistat is a strong CYP3A4 inhibitor. Dose reduction is generally required for CNI, mTOR inhibitors, and statins when used with COBI. Cobicistat may increase SCr via inhibition of renal tubular secretion of Cr.

Abbreviations: CKD, chronic kidney disease; CNI, calcineurin inhibitor; Cr, creatinine; CrCl, creatinine clearance; MPGN, membranoproliferative glomerulonephritis; mTOR, mammalian target of rapamycin; nDI, nephrogenic diabetes insipidus; SCr, serum creatinine.

Integrase inhibitors (bictegravir, cabotegravir, elvitegravir, dolutegravir, raltegravir)

Renal dose adjustment is not required for elvitegravir, dolutegravir (no data on dosing after dialysis), and raltegravir (dose after dialysis).

Bictegravir

- CrCl 30 mL/min or higher: No dosage adjustment is required.
- CrCl less than 30 mL/min: Use is not recommended.

Cabotegravir: no data for CrCl less than 15 mL/min

Elvitegravir: metabolized by CYP3A4, UGT1A1/3. Potential for CNI-drug-drug interactions

Dolutegravir

- Metabolized primarily via hepatic glucuronidation by UGT1A1 with a small contribution from CYP3A4. Significant drug-drug

interaction with CNIs is not expected.

- Dolutegravir may cause an increase in SCr without apparent decrease in renal function, thought to be due to inhibition of tubular secretion of creatinine via the organic cation transporter OCT2 (similar to the interaction seen with cimetidine or trimethoprim).

Raltegravir is not a cytochrome P450 substrate and, therefore, lacks drug-drug interactions with CNIs.

Fusion inhibitors: Enfuvirtide may be associated with membranoproliferative glomerulonephritis (MPGN) pattern of injury. Renal dose adjustment is not required.

CCR5 antagonists (maraviroc)

- Dose adjustment is not required for mild-to-moderate CKD.
- Avoid use in patients with CrCl less than 30 mL/min and those who are dialysis dependent.

Protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir)

- Renal dose adjustment is not required for atazanavir, darunavir, indinavir.
- Renal dose adjustment is probably not required for tipranavir (has not been studied in patients with CKD but renal elimination of tipranavir is negligible).
- No data in CKD: fosamprenavir, lopinavir, nelfinavir
- Not recommended for severe CKD: saquinavir

Nonnucleoside reverse transcriptase inhibitors (NNRTIs): doravirine, delavirdine, efavirenz, etravirine, nevirapine, rilpivirine

- Renal dose adjustment is not required for doravirine, delavirdine, efavirenz, etravirine.
- Nevirapine: GFR 20 mL/min or higher: No dose adjustment is required. Not recommended for GFR less than 20 mL/min.

- Rilpivirine: Use with caution in severe CKD.

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs): abacavir (ABC), didanosine (ddI), emtricitabine, 3TC, stavudine, tenofovir, zidovudine

- Renal dose adjustment is required for ddI, emtricitabine, 3TC, stavudine, TDF, zidovudine, tenofovir alafenamide (not recommended if CrCl <15 mL/min and not on dialysis).
- Renal dose adjustment is not required: ABC.
- NRTIs reported to cause Fanconi syndrome: 3TC, ABC, ddI, and tenofovir.
- NRTIs reported to cause nephrogenic diabetes insipidus: ABC, ddI, tenofovir.
- NRTIs may cause type B lactic acidosis.

Cobicistat is a pharmacokinetic enhancer used in the fixed-dose four-drug combination of elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild).

- Cobicistat can increase SCr via inhibition of tubular secretion of creatinine without affecting the GFR. However, it should be noted that cobicistat is a strong CYP3A4 inhibitor and hence significant dose reduction is generally required with concomitant administration of the CNIs (CsA, Tac), mTOR inhibitors (sirolimus, everolimus), and statins.
- There is enhanced nephrotoxicity with the coadministration of TDF.

Drugs that crystallize and cause urolithiasis

- Protease inhibitors (saquinavir, lopinavir/ritonavir, indinavir, atazanavir, darunavir). Currently, indinavir has largely been replaced by atazanavir and darunavir.
- Indinavir crystals have been described as "plate-like rectangles and fan-shaped or starburst forms."

- Saquinavir is also associated with hypocalcemia and lactic acidosis. Its use is not recommended in patients with severe CKD.

Antihypertensive Selection in Patient Receiving HD

Angiotensin-converting enzyme inhibitors (ACEi)

Dialyzable: captopril, lisinopril
Nondialyzable: benazepril, fosinopril, quinapril

Angiotensin receptor blockers (ARBs) are generally not dialyzable.

β-Blockers

- Carvedilol, labetalol, metoprolol, propranolol, and pindolol are hepatically metabolized. No dose adjustment is needed for patients with CKD.
- Atenolol and sotalol are renally excreted and require dose reduction.

Dialyzable: atenolol, metoprolol, acebutolol, and nadolol
Nondialyzable: carvedilol, labetalol, propranolol, timolol

Calcium channel blockers: Diltiazem, verapamil, amlodipine, and nifedipine are not dialyzable.

NEPHROTOXICITY OF MEDICATIONS

Principles/Mechanisms of Nephrotoxicity

Reduced renal perfusion

Hypovolemia: excessive use of diuretics
Rapid drop in blood pressure (BP) from baseline with antihypertensive agents
Predominant afferent vasoconstriction: nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin, CNI, interleukin-2 (IL-2), iodinated radiocontrast media, sodium glucose cotransporter 2 inhibitors (SGLT2i)
Predominant efferent vasodilatation: ACEi, ARB

SGLT2i can cause an acute transient dip in GFR of up to 20% to 30%, thought to be due to SGLT2i-induced afferent arteriolar vasoconstriction. Nevertheless, several randomized controlled trials (RCTs) and systematic reviews and meta-analyses have demonstrated that SGLT2s reduce the rate of kidney disease progression in patients with CKD, irrespective of diabetes status, primary kidney disease, or kidney function.

- 2022 ADA-KDIGO guidelines for patients with type 2 diabetes mellitus (DM) and CKD: Initiate SGLT2i if estimated GFR (eGFR) is 20 mL/min or higher; continue until dialysis or transplant and/or initiate metformin if eGFR 30 mL/min or higher.
- Contraindications or avoid: type 1 DM (not approved by FDA), history of diabetic ketoacidosis (DKA) or euglycemic DKA, patients *at risk for* or *with a history of* recurrent genital mycotic infections, UTIs, pyelonephritis, urosepsis, neurogenic bladder (or genitourinary abnormalities), chronic hypotension, recurrent volume depletion, lower limb amputation, Fournier gangrene, peripheral vascular disease, recurrent pancreatitis
- Use with caution: concomitant diuretic use (need to adjust diuretic dose to minimize the risk of volume depletion, caloric malnutrition), older patients (need to closely assess volume and nutritional status), alcohol abuse (malnutrition and increased DKA risk)

Amphotericin

- Disruption of endothelial cells leads to both afferent and efferent vasoconstriction (afferent vasoconstriction is more severe than efferent vasoconstriction).
- Afferent vasoconstriction may be due to enhanced tubuloglomerular feedback.
- Injury of medullary collecting tubules leads to poor response to antidiuretic hormone (ADH), poor renal concentrating defect, polyuria, and nephrogenic diabetes insipidus.

Acute tubular injury (ATI)

Direct toxicity to tubules: cisplatin, AG, particularly combination of cisplatin and AG, cephalosporins, amphotericin-B, rifampin, pentamidine, NSAIDs, iodinated radiocontrast media, CNI

Myoglobinuria-induced ATI

- Most common drug class that can cause rhabdomyolysis and myoglobinuria are statins.
- The risk of statin-induced rhabdomyolysis is increased with concurrent use of CsA or gemfibrozil. Rhabdomyolysis associated with Tac and statin use is generally seen in patients on concomitant *diltiazem* therapy (diltiazem is a moderate CYP3A4 inhibitor).

> **NOTE**
>
> CsA is both a substrate and an inhibitor of the cytochrome P450 enzyme system (CYP3A4). Concomitant use of drugs that are extensively metabolized by the CYP3A4 enzyme system (such as statins) can result in a significant increase in statin drug level and, therefore, risk for statin-induced rhabdomyolysis. Tac is a substrate, but not inhibitor, of the CYP3A4 enzyme system (does not affect statin drug level).

- Drugs that cause neuroleptic malignant syndrome (eg, phenothiazines, antipsychotics, narcotics, antidepressants), cocaine, methamphetamine

Hemoglobinuria-induced ATI

Drugs that may cause hemolysis: sulfonamides, dapsone, rifampin, methyldopa, quinidine, procainamide, melphalan, isoniazid, rasburicase, penicillins, cephalosporins, nitrofurantoin, phenacetin

Acute interstitial nephritis

Common drugs that can induce AIN: most antibiotics, NSAIDs, PPIs, cimetidine, thiazides, allopurinol, checkpoint inhibitors (see also **"Immunosuppressive and antineoplastic agents"** section)

Proton pump inhibitors

- PPI-associated AIN and AKI may go unrecognized and present as CKD.

- PPI use is also associated with hyponatremia and hypomagnesemia.
- At-risk individuals for PPI-induced hypomagnesemia have been reported to have a single-nucleotide polymorphism in the apical epithelial magnesium channel TRPM6 in magnesium-absorbing small intestines.

Proximal tubular epithelial cell injury resulting in Fanconi syndrome: lead, cisplatin, AG, tenofovir, 3TC, ABC, ddI, valproic acid, L-lysine supplement (used for antiviral, wound healing properties)

Obstructive uropathy

Microtubular obstruction due to drug crystallization, a.k.a. crystal nephropathy

- Well-described causative agents: sulfadiazine, methotrexate, methoxyflurane, acyclovir, indinavir, nelfinavir, acetazolamide, triamterene, topiramate, zonisamide
- Others: orlistat, oral sodium phosphate preparation, and ciprofloxacin
- Heroin-induced crystal nephropathy developing after a massive amount of heroin injection has been described. Urine microscopy reveals broomstick-like crystals without renal tubular epithelial cells or casts. Electron microscopy demonstrates intratubular crystals with peripheral radiating spicules within tubular epithelial cells.
- Methenamine/sulfonamide combination may lead to the precipitation of sulfonamides with formaldehyde (methenamine is hydrolyzed to formaldehyde in acidic urine). The combination of methenamine/sulfonamide is contraindicated and should not be given to the same patient.

Retroperitoneal fibrosis: methysergide, hydralazine, methyldopa

Small-vessel vasculitis (hypersensitivity angiitis)

Common antibiotics: penicillin G, ampicillin, sulfonamides
Diuretics: thiazides, metolazone
Antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN): propylthiouracil, methimazole, allopurinol, hydralazine, levamisole, D-penicillamine, antitumor necrosis factor-α agents (eg, etanercept, infliximab, adalimumab), phenytoin, sulfasalazine, clozapine, levamisole (cocaine laced with levamisole)

Thrombotic microangiopathy (TMA)

Transplant settings: CsA, Tac, sirolimus, everolimus
Others: mitomycin-c, 5-fluorouracil, quinine, cocaine, clopidogrel

Proteinuria, nephrotic syndrome

Common agents: gold, captopril (this is thought to be specific to captopril, not other ACEi, due to the thiol group in captopril), NSAIDs, D-penicillamine, IFN-α
Histopathology: Drug-induced nephrotic syndrome may present as membranous nephropathy (MN), minimal change disease (MCD), or focal segmental glomerulosclerosis (FSGS). IFN-α may be associated with collapsing FSGS.

Chronic tubulointerstitial disease: NSAIDs, thiazides, lithium, aristolochic acid (AA), germanium. See also **Chapter 6: Tubular, Interstitial, and Cystic Disorders.**

Drugs that may be associated with multiple abnormalities

Diuretics

- Volume depletion (all diuretics, worst with loop diuretics)
- Hypokalemic nephropathy (seen with all agents, except potassium-sparing diuretics)
- Tubulointerstitial nephritis (thiazides, furosemide)
- Vasculitis (thiazides)

- Nephrolithiasis (triamterene, acetazolamide at low urine pH)
- Electrolyte abnormalities, hyponatremia (particularly thiazides), hypokalemia, hyperuricemia (particularly thiazides)

Bisphosphonates

- Kidney injury associated with bisphosphonates:
  - AKI has been reported with IV bisphosphonates, particularly when administered as rapid infusion and frequent doses to patients with malignancy. Biopsy reveals tubular injury with low Na^+-K^+-ATPase expression. Oral bisphosphonates have not been associated with an increased risk of AKI.
  - Collapsing FSGS has been reported with pamidronate, alendronate, zoledronate, and ibandronate.
  - Toxic ATN has been reported, predominantly with zoledronate.
  - Other possible lesions associated with bisphosphonates: chronic interstitial nephritis (CIN) with Fanconi syndrome
- Cardiovascular effects:
  - Discrepancies exist between meta-analyses of RCTs and real-life studies on cardiovascular protection of bisphosphonates (thought to be due to differences in follow-up duration, study populations, and treatment adherence, among others).
  - The association between bisphosphonate use and atrial fibrillation has not been consistently demonstrated in RCTs and observational studies. Equivocal or conflicting data (alendronate, zoledronate). Nonetheless, avoid use in patients at risk for atrial fibrillation.
- Use of bisphosphonates in CKD:
  - FDA warns against the use of bisphosphonates in patients with GFR less than 30 mL/min/1.73 m^2.
  - KDIGO suggests *not* to prescribe bisphosphonate to patients with eGFR less than 30 mL/min/1.73 m^2 without a strong clinical rationale.

Immunosuppressive and Antineoplastic Agents

Methotrexate

- Kidney injury may occur due to intratubular crystallization and obstruction.
- High dose of folinic acid has been shown to revert nephrotoxicity.

Cyclophosphamide

- The use of CYC may be associated with hyponatremia, premature ovarian failure, hemorrhagic cystitis, and bladder cancer. Bladder toxicity, hematologic malignancy (related to total lifetime exposure >36 g), myelofibrosis (>80 g), ovarian failure (>7.5-15 g/m^2 for young to older pediatric patients, 300 mg/kg for adults)
- Toxic metabolite: acrolein

Significant interactions of **CYC** with **other commonly used drugs**

- Allopurinol reduces CYC metabolism.
- CYC may increase bleeding risks with most anticoagulants due to unknown mechanisms.

Management

- Hydration with normal saline
- Administration of mesna to detoxify acrolein and reduce hemorrhagic cystitis risk
- Use of agonist of pituitary gonadotropin-releasing hormone receptors leuprorelin for gonadal protection in women of childbearing age.
- Limit cumulative lifetime dose to less than 36 g to minimize malignancy risk.

Ifosfamide

- Toxic metabolite: chloroacetaldehyde
- Associated with proximal tubular injury, proximal RTA, Fanconi syndrome, nephrogenic diabetes insipidus, ATN

Risks for nephrotoxicity: cumulative dose greater than 90 g/m^2, underlying CKD, concurrent use of other nephrotoxic drugs
Management: supportive, consider mesna

Cisplatin

- Cisplatin disrupts DNA transcription and replication.
- Cisplatin-induced nephrotoxicity is thought to involve free radicals/oxidative stress leading to renal epithelial cell apoptosis and necrosis. Vascular and glomerular injuries may also be seen (TMA).

Toxicity risks: dose related, typically greater than 25 to 33 mg/m^2/wk, concurrent use of AG
Kidney injuries include

- ATN, AIN
- Tubular damage leading to:
  - Salt wasting (Na^+, K^+, Mg^{2+}, Ca^{2+}, PO_4^{2-}); hypomagnesemia can be severe.
  - Fanconi syndrome
  - Nephrogenic diabetes insipidus

Preventive: Normal saline support during cisplatin therapy is key. Other suggested measures include the use of IV sodium-thiosulfate (if >200 mg/m^2 of cisplatin will be administered), methylprednisolone, *N*-acetylcysteine, and antioxidants.
Management: electrolyte replacement as needed

Antiangiogenic agents

- Bevacizumab, a humanized monoclonal antibody (mAb) directed against the vascular endothelial growth factor (anti-VEGF), can lead to glomerular endothelial injury (ie, endotheliosis, swollen vacuolated endothelial cells occluding capillary lumen) and disruption of the glomerular filtration barrier, TMA, hypertension (HTN), and proteinuria resembling preeclampsia.

- Tyrosine kinase inhibitors (TKIs) are agents that block intracellular signal transduction for VEGF receptors. TKI-associated AKI lesions include TMA and AIN. FSGS and MCD have also been reported. Examples of TKI: sunitinib, sorafenib, lenvatinib, pazopanib.

Anti-epithelial growth factor receptors agents

- Anti-epithelial growth factor receptor mAb (eg, cetuximab, panitumumab)
- Used to treat epithelial malignancies
- Associated with hypomagnesemia

Proteasome inhibitors (PI)

- PIs inhibit the normal degradation of cellular proteins. The accumulation of cellular proteins leads to cell dysfunction and death.
- PIs including the reversible agent bortezomib and irreversible agent carfilzomib are used to treat multiple myeloma and plasma cell dyscrasias.
- AKI due to ATN, TMA, and tumor lysis have been reported.
- TMA is typically associated with normal levels of ADAMTS 13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), but low levels have been reported. Patients with carfilzomib-induced TMA may tolerate a switch to bortezomib without TMA recurrence.

Immune checkpoint inhibitors

- Immune checkpoints are regulators of the immune system that serve to prevent the immune system from self-attacking cells indiscriminately. Cancer cells can develop mechanisms to counteract these checkpoints, thereby evading immune attack and cell death. Checkpoint inhibitors have been developed to "activate" the immune system to attack tumor cells. Unfortunately, this activated immune system can simultaneously

lead to the loss of recognition of self-antigens in kidneys and/or unmask a subtle immune response against medications known to precipitate acute interstitial nephritis (AIN), such as PPI or NSAIDs.

- Checkpoint inhibitors in clinical use include anti-programmed cell death antibody (anti–PD-1 antibody) and anti-CTLA4 antibody.
  - Nivolumab and pembrolizumab are anti–PD-1 antibodies: AIN has been reported to occur between 3 and 12 months following drug exposure.
  - Ipilimumab is an anti-CTLA4 antibody: AIN may occur within 12 weeks of drug exposure.
  - Mild AIN along with glomerular lesions such as MN, MCD, TMA, pauci-immune GN, immune complex glomerulonephritis (ICGN), C3GN, IgAN, or amyloid A have been reported.
- Most cases of AIN respond to GCs.

Chimeric antigen receptor (CAR)-T cells

- Patient's own T cells are genetically engineered to express a synthetic receptor that binds a tumor antigen. CAR-T cells are then infused back into the patient's bloodstream where they recognize specific proteins (antigens) on the surface of cancer cells and destroy them.
- CAR-T cells directed against CD-19 include axicabtagene ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel.
- CAR-T cell therapy can lead to cytokine release syndrome with resultant systemic vasodilation, multiorgan hypoperfusion, and AKI.
- Electrolyte disturbances including hyponatremia (possibly due to IL-6–mediated increase in ADH), hypophosphatemia (due to IL-6–mediated increase in FGF-23), and hypokalemia (increased cortisol) may be seen.

Immune-modulatory drugs: lenalidomide and pomalidomide

- Used to treat multiple myeloma and primary amyloidosis
- Associated with AKI, MCD, and DRESS syndrome (Drug Reaction with Eosinophilia, Rash and Systemic Symptoms)

Vemurafenib and dabrafenib: B-rapidly Accelerated Fibrosarcoma (BRAF) oncogene inhibitors

- Used to treat BRAF V600E mutation–positive melanoma, colorectal carcinoma
- Associated with AIN and ATN

Poly-ADP ribose polymerase inhibitors (PARPi)

- PARPi are used in gynecologic cancers, breast, prostate, and pancreatic cancers.
- PARPi include olaparib, rucaparib, niraparib, and talazoparib.
- The increase in SCr with the use of PARPi is thought to be related to decreased tubular secretion of creatinine, rather than direct tubular toxicity.

Cyclin-dependent kinase 4/6 inhibitors (CKDi)

- CKDi (eg, abemaciclib used in the treatment of breast cancer) inhibit normal cell cycle progression.
- The increase in SCr with the use of CKDi may be due to decreased tubular secretion of creatinine and/or true nephrotoxicity.

Interferons (IFNs)

- IFNs are immune-modulatory agents that have antiviral, antiangiogenic (anti-VEGF effect), and antiproliferative effects.
- Clinically, INFs are used to treat viral infections (eg, hepatitis C), cancers (eg, non-Hodgkin lymphoma), and autoimmune disease (eg, multiple sclerosis).

- Different patterns of kidney injury have been reported with different IFN types, even after prolonged and well-tolerated therapy.

Adverse effects and kidney lesions associated with IFN

- Endothelial damage: new-onset headaches, HTN, malignant HTN, proteinuria, AKI, TMA, clinical syndrome similar to preeclampsia
- Glomerular injury: podocytopathy (FSGS, MCD, MN, MPGN pattern of injury)
- Tubular injury: ATN, AIN, systemic lupus erythematosus (SLE)-like syndrome
- SLE-like syndrome

Management: IFN discontinuation, supportive care

Supplements/Herbs (Toxic Agents): Renal/Urological Manifestations

Aristolochia species (AA): progressive CIN, proximal tubular injury, uroepithelial malignancies. Others: Fanconi syndrome, AKI due to ATN

Balkan endemic nephropathy (BEN): resembles aristolochic acid nephropathy (AAN) in terms of CIN and association with uroepithelial malignancies, but its rate of disease progression spans over 20 to 30 years compared to a much more rapid course of months to 2 years with AAN.

- Prospective monitoring in endemic areas showed that tubular proteinuria is usually the first manifestation of BEN. Early tubular dysfunction can also lead to glucosuria, aminoaciduria, increased uric acid excretion, and impaired urinary acidification.
- Chronically, there is progressive urinary concentrating defects with renal salt wasting and associated polyuria. Such defect may precede GFR decline and progression to ESKD.

- The inciting agent is unknown but has been suggested to be AA or other regional toxins (eg, mycotoxins, heavy metals, viruses).

Bladderwrack: a large brown algae used as food or flavoring agent in Japan and Europe (associated toxins are thought to be heavy metal contamination): CIN

Cat's claw: acute allergic tubulointerstitial nephritis

Chaparral tea: made of leaves from the Native American shrub creosote (nordihydroguaiaretic acid): renal cysts and renal cell carcinoma

Cranberry: cranberry juice or cranberry concentrate tablets (oxalic acid): interstitial nephritis, oxaluria, oxalate stones

Djenkol (djenkolic acid): nephrolithiasis

Echinacea species, a.k.a. coneflower (arabinogalactan): RTA

Germanium: tubular degeneration with minor glomerular abnormalities

Licorice (glycyrrhizic acid): HTN, hypokalemia, hypokalemic nephropathy, metabolic alkalosis

L-Lysine: Fanconi syndrome and tubulointerstitial nephritis

Ma Huang (Ephedras): HTN, nephrolithiasis secondary to *Ephedra*, norephedrine, and pseudoephedrine stone

Pennyroyal: hemorrhagic kidneys, hepatorenal syndrome, and associated ATN

Rhubarb (anthraquinone): CIN, oxalate crystal–induced AKI, oxalate nephropathy

Star fruit: oxalate stones, oxalate nephropathy

Willow bark (salicin, the precursor of salicylate): renal papillary necrosis

Wormwood oil: AKI secondary to rhabdomyolysis

Yellow oleander: tubular necrosis with vacuolization in glomerular spaces in the setting of hepatorenal syndrome

Yohimbine (yohimbe): lupus nephritis

Iodinated Contrast and Other Imaging Agents

See Contrast-associated AKI in **Chapter 11: Acute Kidney Injury/ICU Nephrology**.

Nephrotoxicity of Illicit Drugs

Heroin and other IV drug use

- Nonspecific histopathologic findings: arteriosclerosis, calcifications, interstitial fibrosis, tubular atrophy
- Heroin-specific causes for kidney injury: renal amyloid, FSGS, rhabdomyolysis

Ecstasy (methylenedioxymethamphetamine [MDMA]), *N*-benzylpiperazine (BZP), a.k.a. "party pills"

- Both produce stimulant, euphoric effects.
- Users may develop hyperthermia, rhabdomyolysis, kidney failure, interstitial nephritis, hyponatremia, and cerebral edema.
- Other renal/electrolyte effects: hyperkalemia, metabolic acidosis, urinary retention, mesangial proliferative GN

Cocaine may cause renal ischemia, infarction, rhabdomyolysis, severe vasoconstriction, HTN. Others: acute myocardial infarction, accelerated atherosclerotic disease, arrhythmias, hemorrhagic or ischemic stroke

Levamisole-laced cocaine

In addition to cocaine-associated complications above, ANCA-associated GN may be seen in patients using cocaine that is laced with levamisole.

"Bath salts"

- White powder containing 3,4-methylenedioxypyrovalerone
- May be inhaled, ingested, or injected
- May cause fulminant liver failure, rhabdomyolysis, kidney failure, disseminated intravascular coagulopathy
- Supportive therapy

Cannabis and synthetic cannabinoids

With the legalization of cannabis in several states in the United States, cannabis has become the second most commonly used psychotropic drug in the United States, second only to alcohol.

Synthetic marijuana (cannabinoids)

- Formulations/street names: K2, Spice, herbal incense, Bonsai, Cloud 9, Mojo, Arizona, Black Mamba, Lava Red, Banana Cream Nuke
- Medical uses: chronic pain in ESKD, anxiety, insomnia, chronic neuropathic pain, refractory nausea and vomiting. Therapeutic benefits should be weighed against risks.
- Signs and symptoms of acute cannabis intoxication: hunger, tachycardia, tachypnea, HTN, orthostatic hypotension, ocular erythema, dry mouth, nystagmus, ataxia, slurred speech, acute psychosis
- Complications of cannabinoids:
  - Associated with hypokalemia, AKI due to ATN, AIN, or both
  - Creatinine phosphokinase is usually normal or only slightly elevated, but cases of rhabdomyolysis have been reported.

- Synthetic cannabinoid and concomitant overuse of quetiapine can cause rhabdomyolysis, thought to be due to their synergistic effect in mediating muscle injury.
- Chronic use may be associated with cannabinoid hyperemesis syndrome where patients may find relief with taking hot showers.

- Management:
  - Largely supportive
  - A tapering course of steroid may be beneficial in AIN cases.

NEPHROTOXICITY OF ENVIRONMENTAL AND OCCUPATIONAL AGENTS

Lead (Pb) Nephropathy

Mechanism of disease

- Pb is absorbed in proximal tubular cells where it binds to specific Pb-binding proteins, which facilitate entry into mitochondria and nuclei.
- Pb-protein complexes cause mitochondrial injury and dysfunction, leading to reduced adenosine triphosphate (ATP) production, ineffective tubular transports (Fanconi syndrome), and inhibition of various enzymes, including aminolevulinic acid (ALA) synthase and ferrochelatase, a heme-containing hydroxylase. The latter interferes with the conversion of 25(OH)- to 1,25$(OH)_2$-vitamin D.
- Major metabolic effects of chronic Pb exposure include HTN and hyperuricemia. The former is thought to be due to alterations in the vasoactive arachidonic acid metabolites favoring vasoconstriction and the latter to enhanced tubular reabsorption and reduced tubular secretion of uric acid.

Acute Pb exposure

- Multiorgan involvement including headaches, malaise, peripheral neuropathy, poor memory, encephalopathy, seizures, coma,

colicky abdominal pain, nausea, vomiting, constipation, anemia, muscle weakness, Fanconi syndrome

- In acute Pb nephropathy, Pb-protein complexes may be seen as intranuclear inclusions.

Chronic Pb exposure

Clinical manifestations

- Gout, HTN
- Renal manifestations:
  - The kidneys are typically contracted with a granular surface appearance.
  - Chronic tubulointerstitial nephritis
- Notable physical finding: gingival lead line

> **NOTE**
>
> Although hyperuricemia is common in CKD, gout is not a common manifestation of CKD. All patients with CKD and gout should be tested for Pb. Bone Pb levels may be better correlated with HTN than blood Pb levels.

Differential diagnosis: uric acid nephropathy, arsenic exposure, CIN, radiation nephritis, chronic glomerulosclerosis

Diagnostic testing for chronic Pb toxicity

- Nonspecific laboratory findings: anemia of chronic disease, microcytic hypochromic anemia, basophilic stippling of red blood cells, normal anion gap metabolic acidosis, hypophosphatemia, Fanconi syndrome, elevated SCr
- Pb-specific testing:
  - Increase blood and urinary ALA due to inhibition of erythrocyte aminolevulinic acid dehydratase (ALAD) by Pb. Iron deficiency must be ruled out first since it can increase ALAD activity and mask Pb-induced reduction in ALAD activity.
  - Blood Pb levels:

- Significantly elevated in acute exposure but may not be elevated in chronic exposure
- Assessment for total body Pb accumulation is recommended for chronic exposure: (1) calcium disodium edetate (ethylenediaminetetraacetic acid [EDTA]) chelation test (given at 1 g intramuscularly × two doses 12 hours apart or 1 g IV × one dose to immobilize stored Pb) followed by 24-hour urine collection to measure for Pb-EDTA. In patients with CKD, urine collection should be done over 3 to 6 days. (2) Radiographic fluoroscopy, a procedure whereby x-ray excitation of skeletal Pb atoms leads to fluorescence that can be detected and calculated.

Management: chelation therapy with EDTA

Organic Solvents

- Chronic organic solvent exposure has been linked to various glomerular diseases including RPGN with or without anti-glomerular basement membrane antibodies, MN, IgAN, and FSGS.
- Limited studies suggest that organic solvent exposure may worsen the progression of preexisting GN rather than contributing to the development of GN.
- Organic solvents that have been implicated in causing or worsening preexisting GN include products or processes that contain solvents or petroleum products such as paint, printing ink, adhesives, degreasers, cleaning agents, aerosols, pesticides, and gasoline.

SPECIFIC DRUG ADVERSE EFFECTS OF INTEREST TO THE NEPHROLOGIST

Drug Metabolite Accumulation in Patients With CKD

Drug metabolite accumulation that can lead to significant adverse effects in patients with reduced kidney function include the following:

- Allopurinol → oxypurinol (tubulointerstitial nephritis)
- Glyburide → hydroxyglibenclamide (hypoglycemia)
- Meperidine (pethidine) → normeperidine (seizures, myoclonus, altered mental status, opisthotonos, respiratory depression, psychosis)
- Morphine → morphine-3-glucuronide and morphine-6-glucuronide (altered mental status, seizures, respiratory depression)
- Nitroprusside → thiocyanate (cyanide toxicity)
- Tramadol → *O*-desmethyltramadol (M1) (altered mental status, seizures, respiratory depression)
- Venlafaxine → *O*-desmethylvenlafaxine (altered mental status). Other adverse effects relevant to nephrologists: HTN (may be accelerated), orthostatic hypotension, prolonged QT

Pain Control in CKD

Narcotics that may be used in advanced CKD (stages 4-5)

Fentanyl, hydromorphone, methadone, buprenorphine

Fentanyl

- Fentanyl is rapidly metabolized in the liver, with more than 90% eliminated by biotransformation to *N*-dealkylated and hydroxylated inactive metabolites.
- Less than 7% of the administered dose is excreted unchanged in the urine, and less than 1% is excreted unchanged in the feces.
- There appears to be no clinically significant accumulation of fentanyl in patients with advanced CKD (black box warning of respiratory arrest, particularly in opioid-naïve patients).

Hydromorphone

- Hydromorphone is extensively metabolized via glucuronidation in the liver, and only a small amount of hydromorphone is excreted unchanged in the urine.
- There is no clinically significant opioid toxicity when hydromorphone is given at low doses.

Use with caution in advanced CKD: Oxycodone

Narcotics that are not recommended for use in advanced CKD

Tramadol, morphine, codeine, meperidine, propoxyphene

Tramadol

- Although tramadol is primarily hepatically metabolized, its metabolites are eliminated by the kidneys.
- Approximately 30% of the dose is excreted in the urine as unchanged drug and 60% as metabolites.
- The accumulation of its active metabolite, *O*-desmethyltramadol, can lead to seizures and respiratory depression.

Morphine: rapid accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity (sedation, confusion, myoclonus, seizures, respiratory depression)

Codeine and dihydrocodeine (semisynthetic derivative of codeine):

- Codeine is metabolized in the liver by the enzyme CYP2D6 to its active metabolite morphine, which accumulates in CKD.
- Potential adverse effects: severe hypotension, respiratory arrest, narcolepsy

Reversal of opioid intoxication: Naloxone may be used at normal dose.

Agents use for neuropathic pain

Gabapentin and pregabalin

- Gabapentin and pregabalin are extensively cleared by the kidneys.
- Dose adjustment in CKD is required.
- Accumulation and toxicity can lead to reduced consciousness, confusion, ataxia, myoclonus, tremulous, and asterixis.
- **FDA warning:** Gabapentin or pregabalin use either alone or with opioids (or other drugs that depress the CNS) can lead to life-

threatening respiratory failure and increased risk of opioid overdose death.

- Older patients and those with underlying respiratory impairment are also at increased risk for respiratory failure.
- Gabapentin and pregabalin are dialyzable.

Neuromuscular-blocking agents are renally excreted and have increased $t_{1/2}$ in patients with ESKD.

IMMUNOSUPPRESSIVE THERAPY (SEE ALSO CHAPTER 9: KIDNEY TRANSPLANTATION)

Induction Therapy

Antithymocyte globulin (ATG)

- Polyclonal antibodies that induce T-cell depletion
- Associated with cytokine release syndrome with flulike symptoms and myelosuppression with leukopenia and thrombocytopenia. Premedications are required.

Basiliximab (monoclonal IL-2 antagonists): well tolerated; no known drug interaction; no dose adjustment is necessary for renal impairment

Maintenance Therapy

Calcineurin inhibitors

CNIs including CsA and Tac inhibit the dephosphorylation of the nuclear factor of activated T-cell (NFAT) molecules, which results in reduced IL-2 synthesis.

CsA is derived from the fungus *Tolypocladium inflatum*.

- Plasma concentration at 2-hour postadministration better correlates with the area under the curve (AUC) compared with that of 12-hour trough levels.
- CsA metabolism and Cl

    - GI absorption varies depending on food fat content, GI motility (diabetic gastroparesis), diarrhea. Microemulsion formulation (Neoral) improved pharmacokinetic properties, but not proven graft survival. Oral to IV conversion is one third of oral dose.
    - CsA is not dialyzable. No dose adjustment is necessary for renal impairment or dialysis.
    - CsA is a substrate as well as an inhibitor of both CYP3A4 and P-glycoprotein.
- CsA is predominantly metabolized by cytochrome P450 3A4.
    - St John wort induces cytochrome P450 3A4 and can lead to subtherapeutic CsA level and rejection.
    - In contrast, grapefruit juice, pomegranate, and the nondihydropyridine calcium channel blockers diltiazem and verapamil are moderate CYP3A4 inhibitors and can increase CsA levels and cause CsA toxicity. Changing the dose of diltiazem or verapamil is equivalent to changing CsA dosage. CNIs and drug-drug and drug-food interaction are also discussed in **Chapter 9: Kidney Transplantation**.
- Side effects:
    - HTN, fluid retention, hyperchloremic metabolic acidosis, hyperkalemia, chronic nephrotoxicity, rhabdomyolysis, hyperuricemia, hypomagnesemia (CsA, Tac, sirolimus can cause hypomagnesemia by inducing urinary magnesium wasting—thought to be due to downregulation of the Mg^{2+} transient receptor potential 6 channel at the distal convoluted tubule)
    - Hirsutism and gingival hyperplasia are common with CsA, but not with Tac. Gingival hyperplasia may be treated with azithromycin.
    - Rare adverse effect: TMA
- Histopathologic findings in chronic CNI toxicity: obliterative arteriopathy, tubular atrophy, and classic "striped" interstitial fibrosis, afferent arteriopathy

Tac (FK-506) is derived from the fungus *Streptomyces tsukubensis*.

- Tac metabolism and Cl:
  - Oral bioavailability is highly variable (5%-67%). Drug levels require close monitoring with dose adjustments.
  - Tac is highly bound to albumin, α-1 acid glycoprotein, and erythrocytes.
  - Levels should be measured from whole blood, not plasma.
  - Metabolism is via cytochrome P450 CYP3A4 and CYP3A5 mainly in the liver and the gut. Inconsistent presystemic gut metabolism likely contributes to the intrapatient variation in drug levels that are seen clinically. Polymorphisms in CYP3A5 significantly increase Tac metabolism and Cl. CYP3A5 expressors require much larger doses of Tac compared to nonexpressors to achieve therapeutic blood concentration
  - Oral to IV conversion is one third of total oral daily dose. Sublingual dose is one half the oral dose.
  - Tac is not dialyzable. No dose adjustment is necessary for renal impairment or dialysis.
- Most drug interactions are similar to those of CsA (see also **Chapter 9: Kidney Transplantation**).
- Common adverse effects:
  - Nephrotoxicity (similar to CsA: striped interstitial fibrosis, arteriolar hyalinosis), post-transplantation diabetes mellitus (PTDM), hair loss, neurotoxicity, hyperkalemia, hyperuricemia, hypomagnesemia
  - HTN and hyperlipidemia (both are less severe compared with CsA)

NOTE

Enterocolitis can significantly increase Tac levels due to reduced presystemic metabolism in gut wall via P-glycoproteins and CYP3A4/5.

Antiproliferative agents

Azathioprine (AZA)

- AZA is an imidazole analog of 6-mercaptopurine that inhibits both de novo and salvage pathways for T- and B-lymphocyte proliferation.
- Oral bioavailability is 50% to 60%.
- Major side effects: bone marrow suppression, veno-occlusive disease, pancreatitis
- Can be used in pregnancy

NOTE

Avoid or reduce dose (ie, 0.5 mg/kg/d) AZA in patients on allopurinol. Allopurinol interferes with the metabolism of AZA, which leads to a significant increase in 6-mercaptopurine levels and resultant severe bone marrow suppression (pancytopenia).

Mycophenolic acid (MPA)

- MPA inhibits de novo purine biosynthesis in both B and T cells via noncompetitive inhibition of inosine monophosphate dehydrogenase type II.
- Formulated as MMF (CellCept or generic formulation) or enteric-coated mycophenolate sodium (Myfortic). MMF is rapidly converted via plasma and hepatic esterases to MPA, the active form. Mycophenolate sodium is thought to reduce GI intolerance due to its delayed absorption, which occurs in the lower GI tract versus gastric absorption with MMF.
- MPA is used as adjunctive immunosuppressive therapy to improve long-term allograft survival as well as to reduce acute rejection in kidney transplantation.
- Major side effects: GI intolerance, anemia, leukopenia
- Not for use during pregnancy: switch MPA to AZA during pregnancy.

- Level monitoring of mycophenolate is not necessary since plasma concentration does not seem to correlate with the incidence of acute rejection or side effects.
- CsA inhibits the recirculation of hepatically activated MPA back into the gut for absorption, thereby reducing MPA levels. Tac does not block this hepatic recirculation of MPA. Because of this difference, CsA-to-Tac switch may result in increased MPA levels.

mTOR inhibitors

- mTOR inhibition leads to cell cycle arrest at G1 and inhibition of T-cell proliferation.
- Sirolimus and everolimus are mTOR inhibitors.
- mTOR inhibitors are used in combination with low-dose CNI or CNI-avoidance protocols.
- Adverse effects: myelosuppression (thrombocytopenia), delayed wound healing, lymphedema, hyperlipidemia, proteinuria (FSGS), interstitial pneumonitis

Pregnancy and immunosuppressive therapy

- Drugs with limited risk for congenital anomalies: prednisone, CsA, Tac, AZA
- Immunosuppressive agents that are contraindicated in pregnancy: mycophenolate, sirolimus, everolimus (see **Chapter 9: Kidney Transplantation**)

ANTICOAGULANTS, ANTIPLATELETS, THROMBOLYTICS, AND HEMOSTATICS

Parenteral Anticoagulants

Unfractionated heparin (UFH)

- Half-life is slightly prolonged in patients with renal impairment, particularly at higher doses. However, UFH may be started at normal dose with dose titration based on activated partial thromboplastin time.

- Antidote: protamine sulfate

Low-molecular-weight (LMW) heparin

- LMW heparin includes enoxaparin, dalteparin, tinzaparin.
- Smaller LMWs are more dependent on renal Cl, thus may accumulate in CKD.
- Bleeding risk does not appear to be associated with the type of heparin use, but on the degree of uremia, increased age, concurrent treatment, and comorbidities.
- Anti-Xa monitoring for LMW heparin: predose (trough) and peak (2-4 hours postdose) before and after the third dose, then follow twice weekly. Anti-Xa activity level (prophylactic dosing 0.1-0.3; therapeutic 0.4-1.0 U/mL)

Enoxaparin has the lowest MW of all and requires dose reduction if eGFR is less than 30 mL/min.
Dalteparin: No dose adjustment is needed; anti-Xa level monitoring is advised for eGFR less than 30 mL/min.
Tinzaparin has the largest MW of all LMW.

- No dose reduction is needed if eGFR is greater than 20 mL/min.
- Dose adjust per anti-Xa level if eGFR is less than 20 mL/min.
- Drug accumulation may cause excessive bleeding, not easily reversed.

Other parenteral anticoagulants

Fondaparinux, bivalirudin

- These anticoagulants accumulate in renal impairment.
- Their use should be avoided or dose reduced in the setting of renal function impairment.
- Fondaparinux: may be used in patients with CrCl greater than 30 mL/min, but may accumulate and increase bleeding risk

Argatroban

- Inhibits coagulation factor IIa (direct thrombin inhibitor)

- Hepatically cleared; no dose adjustment is needed for CKD.
- Avoid use in liver patients.

Prostacyclins (epoprostenol, iloprost, selexipag, treprostinil)

- Potent inhibitors of platelet aggregation
- Primary use is in the treatment of pulmonary HTN.
- May be used to prevent platelet aggregation in HD circuits
- These agents are unaffected by renal impairment.
- Selexipag use should be avoided in patients with severe liver disease.

Oral Anticoagulants

Warfarin

- Vitamin K antagonist
- 90% protein bound (poor dialyzability)
- Long $t½$ (40 hours); more than 90% renal elimination
- Antidote: vitamin K (phytonadione)
- The use of warfarin may be associated with calcific uremic arteriopathy, a.k.a. calciphylaxis, in dialysis patients and warfarin-related nephropathy, a.k.a. anticoagulant-related nephropathy, in patients with CKD (see **Chapter 4: Chronic Kidney Disease** for the former and **Chapter 6: Tubular, Interstitial, and Cystic Disorders** for the latter).

Direct oral anticoagulants (DOACs). Summarized in **Table 10.2**.

Table 10.2 Direct oral anticoagulants

	RivaroXaban (Xarelto)	ApiXaban (Eliquis)	EdoXaban (Savaysa)	Dabigatran (Pradaxa)
Coagulation target	Xa	Xa	Xa	Thrombin
Protein binding	>90	80-90	55	35

	RivaroXaban (Xarelto)	ApiXaban (Eliquis)	EdoXaban (Savaysa)	Dabigatran (Pradaxa)
(%)				
Drug-drug interactions	• P-gp inhibitors can reduce metabolism of DOACs (eg, clarithromycin, verapamil, ombitasvir- or ritonavir-containing drug combination). • P-gp inducers can increase metabolism of DOACs (eg, St. John's wort, rifampin, phenytoin). • Strong CYP3A4 inhibitors can reduce metabolism of some DOACs (eg, clarithromycin, ombitasvir- or ritonavir-containing drug combination). • Strong CYP3A4 inducers can increase metabolism of some DOACs (eg, carbamazepine, phenytoin, rifampin). • Inhibition of CYP3A4 without P-gp inhibition may increase apixaban and rivaroxaban effect but to a lesser extent than dual inhibition of CYP3A4 and P-gp. (CYP3A4 inhibitors that do not inhibit P-gp may include diltiazem, fluconazole, voriconazole.)			
Contraindicated drugs	Rifampin, ritonavir	Rifampin	Dronedarone	Cobicistat, rifampin, dronedarone, ketoconazole
Surgery hold time	24 h	24-48 h	24 h	CrCl >50: 1-2 d CrCl <50: 3-5 d
Renal clearance (%)	60-70	25-30	50	85
Dialyzability	No	No	No	Yes
Use in advanced CKD	• Reduce dose for CrCl 15-30. • Avoid use for CrCl <15 and dialysis. • Discontinue use during	• No dose adjustment if CKD is the only factor. • Half-dose if ≥2 of the following: Cr ≥1.5	• Half-dose for CrCl 15-50 • Use not recommended for CrCl <15. • HD does not significantly clear edoxaban.	• 75 mg bid for CrCl 15-30 • Dosing not established for CrCl <15 or dialysis

	RivaroXaban (Xarelto)	ApiXaban (Eliquis)	EdoXaban (Savaysa)	Dabigatran (Pradaxa)
	AKI episode.	mg/dL, age ≥80 y, or body weight ≤60 kg • Safety data for dialysis are lacking.		
Antidote/reversal agent	Andexanet alfa 4-factor PCC	Andexanet alfa 4-factor PCC	Andexanet alfa 4-factor PCC	Idarucizumab

• In general, DOACs are noninferior compared to vitamin K antagonists (VKAs) in reducing stroke/thromboembolic event, and all-cause and vascular mortality. However, edoxaban should NOT be used in patients with CrCl of greater than 95 mL/min. In the ENGAGE AF-TIMI 48 study, patients with atrial fibrillation who do not have heart valve disease with CrCl of greater than 95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin.

• DOAC is associated with an approximately 50% reduction in intracranial hemorrhage risk and lower risk of vascular calcification and anticoagulant-associated nephropathy (aka warfarin-related nephropathy).

• Compared to VKAs: DOACs are associated with an increased risk for gastrointestinal bleed (GIB), except for apixaban. The use of a proton pump inhibitor or other gastroprotective drugs seems reasonable in individuals with an increased risk for GIB.

• Continuous venovenous hemodiafiltration (CVVHD) may be beneficial in severe cases of dabigatran overdose.

Abbreviations: 4-factor PCC, four-factor prothrombin complex concentrate is a pathogen-reduced, lyophilized concentrate that contains therapeutic amounts of at least four coagulation factors, including factors II, VII, IX, and X; AKI, acute kidney injury; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; HD, hemodialysis; P-gp, P-glycoprotein.

DOACs include direct factor Xa inhibitors and direct thrombin inhibitors.

Anti-Xa directly binds to factor Xa and prevents factor Xa from cleaving prothrombin to thrombin (rivaro**Xa**ban, api**Xa**ban, edo**Xa**ban).

- Edoxaban should NOT be used in patients with CrCl greater than 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial

fibrillation patients with CrCl greater than 95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin.

- Antidote for anti-Xa: andexanet alfa. Only for use in patients with life-threatening bleeding or those who require emergency surgery. Increased risk of thrombotic events after its use. Alternative option: four-factor prothrombin complex concentrate (four-factor PCC). The four-factor PCC contains the human coagulation factors II, VII, IX, and X.

Antithrombin directly binds to thrombin, thereby preventing thrombin from cleaving fibrinogen to fibrin.

- Dabigatran
  - Antidote for dabigatran: Idarucizumab (Praxbind) can be used for emergency reversal of the anticoagulant effect of dabigatran. If idarucizumab is not available, an activated PCC may be a reasonable alternative.
  - For CrCl 15 to 30 mL/min: Dose reduction recommended.
  - For CrCl less than 15 mL/min or ESKD: Avoid. Warfarin remains the anticoagulation of choice due to the lack of safety data for DOACs in this subpopulation.
- Other orally administered direct thrombin inhibitors: melagatran, ximelagatran

NOTE

DOAC use is contraindicated in renal transplant wait-listed patients. For planned living donor transplantation, DOAC can be transitioned to warfarin.

Antiplatelet Agents

Aspirin, dipyridamole, clopidogrel, prasugrel, ticagrelor

No dosage adjustment is required, although patients with CKD are often more susceptible to bleeding.

GIIb/IIIa Inhibitors (Eptifibatide, Tirofiban, Abciximab)

GIIb/IIIa inhibitors inhibit the final common pathway of platelet-thrombus formation.

Eptifibatide, tirofiban

- Renally excreted and have been associated with bleeding in patients with renal impairment

Abciximab

- Cleared by platelet binding
- No dosage adjustment is required.

Thrombolytic Agents

Streptokinase, anistreplase, and alteplase: may be used but the increased bleeding risk should not be overlooked

Tenecteplase: Renal dose adjustment data are not available.

Urokinase: used for clot dissolution and restoring dialysis catheter patency

Hemostatic Agents

Protamine, vitamin K: do not require dose adjustment

Tranexamic acid: Dose reduction is required in moderate-to-severe renal impairment.

DRUG INTERACTION/ADVERSE EFFECTS (OTHER THAN NEPHROTOXICITY)

Colchicine

- Colchicine is associated with an increased risk of vacuolar myopathy and polyneuropathy in patients with CKD, use of high dose, or concurrent use of myotoxic agents.
- Renal dose adjustment is required.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- With the exception of paroxetine (Paxil), most SSRIs do *not* require dose adjustment.
- SSRIs have an increased risk of hyponatremia and GI bleed when taken with NSAIDs.

Anticonvulsants

Most newer generation anticonvulsants require dose reduction: gabapentin, felbamate, levetiracetam (Keppra), pregabalin (Lyrica), topiramate, zonisamide.

Phenytoin

No dose reduction is generally required. However, monitoring free instead of total phenytoin level is recommended due to reduced protein binding with uremia. While reduced protein binding increases free drug level, the increased free drug level per se leads to increased plasma Cl by hepatic P450. The net alteration in free drug level is therefore difficult to gauge.

Lamotrigine does not require dose reduction.

Methyldopa, α-Blockers, Clonidine, and Minoxidil

- All are renally cleared.
- Clonidine accumulates in advanced CKD and can lead to severe bradycardia or even asystole if used in high dose and in combination with β-blockers.

Minoxidil

- Minoxidil is a potent direct-acting peripheral vasodilator that leads to increased renin-angiotensin-aldosterone system (RAAS) activity, cardiac output, and salt and water retention. Associated side effects include tachycardia and peripheral edema.
- Because of reflex tachycardia and salt and water retention, the use of minoxidil typically requires the concurrent use of a β-blocker and diuretic for optimal antihypertensive effect.
- Warning: Minoxidil can cause pericardial effusion, occasionally progressing to tamponade and exacerbation of angina pectoris. Minoxidil use should be reserved for patients with refractory HTN.

PPIs can reduce GI absorption of MMF due to reduced acid-dependent dissolution of MMF (CellCept) prior to absorption, but not enteric-coated mycophenolate sodium (Myfortic), which is absorbed at neutral pH in the small intestines.

Use of ganciclovir, valganciclovir, and/or co-trimoxazole in combination with MMF or AZA can increase myelosuppressive risk.

Amlodipine increases simvastatin blood levels, hence the risk of rhabdomyolysis. Both amlodipine and simvastatin are metabolized by P450 3A4.

Barbiturate coma therapy (BCT) with thiopentone. Hypokalemia, a potentially life-threatening complication, has been reported to occur in up to 25%. Hypokalemia is thought to be due to increased cellular uptake. The severe rebound hyperkalemia following discontinuation of thiopentone is due to the reshifting of intracellular space and high doses of potassium supplements during the hypokalemic phase. Gradual tapering of thiopentone has been suggested to reduce the risk of rebound hyperkalemia.

CORONAVIRUS DISEASE 2019 (COVID-19) DRUG THERAPY AND DRUG-DRUG INTERACTION/ADVERSE EFFECTS

Nirmatrelvir-Ritonavir Drug Combination (Paxlovid)

- Both nirmatrelvir and ritonavir are CYP3A4 substrates. Ritonavir is a potent CYP3A4 inhibitor. Ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (eg, St John wort, rifampin). Concomitant use of Paxlovid in this setting may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment against COVID-19 ineffective. Consider alternative COVID-19 therapy.
- The use of nirmatrelvir-ritonavir combination therapy can result in markedly elevated CNI or mTOR inhibitor levels and nephrotoxicity. Hence, Paxlovid use should be **avoided** in patients receiving CNI or mTOR inhibitor therapy (ie, Tac, CsA, sirolimus, or everolimus).

Remdesivir

- Limited studies suggest that remdesivir use can result in a significant increase in CNI levels, and hence CNI nephrotoxicity. In one retrospective study of 61 solid organ transplant recipients (56 were on Tac and 5 on CsA), a median increase in Tac level of nearly 85% after starting remdesivir was observed in 58 of 61 patients. No significant change in CNI levels was observed in three patients. The median increase in Tac level was more pronounced in lung and kidney recipients than in heart recipients (96.5% vs 93.9% vs 64.6%). The median time to maximum increase in Tac trough levels was 3 days, and the levels returned to baseline approximately10 days after completion of remdesivir treatment (77.1% completed a 5-day course).

DIALYSIS AND OTHER TREATMENT OF POISONINGS

Pharmacokinetics of toxin removal by various dialytic methods are similar to those outlined for drug dialyzability. In addition, there are a few other extra considerations.

Electrolytes: Electrolyte and acid-base disturbances in patients requiring HD for poisons are not necessarily similar to those seen

with ESKD (ie, serum concentrations of K^+, HCO_3^-, Ca^{2+}, Mg^{2+}, and PO_4^{2-} may be relatively normal). Dialysate should, therefore, reflect patient needs. IV Mg^{2+} and PO_4^{2-} supplements may be necessary.

Extracorporeal Toxin Removal Systems

Hemodialysis

- HD is the treatment of choice for water-soluble drugs, particularly those that have LMW and low protein binding. Such agents diffuse rapidly across the dialyzer membrane. High MW drugs are less well removed because they diffuse more slowly across dialyzer membranes. High-flux membranes and hemodiafiltration may improve their removal rates.
- Drugs removable by HD: salicylates, lithium, methanol, ethylene glycol, isopropyl alcohol, theophylline, valproic acid, methotrexate, phenobarbital, metformin, gabapentin, pregabalin, levetiracetam, acyclovir
- Although acetaminophen (paracetamol) is removed by dialysis or hemoperfusion, *N*-acetylcysteine is the treatment of choice for acetaminophen toxicity/poisoning. *N*-Acetylcysteine has been suggested to prevent or alleviate drug-induced hepatotoxicity by restoring hepatic glutathione stores.

Hemoperfusion

- This is a form of dialysis where a cartridge containing an adsorbent material such as activated charcoal or resin is added to the circuit to compete for binding and removal of albumin-bound toxins from circulation. Hemoperfusion has become less widely available since the advent of high-flux dialysis.
- Hemoperfusion may be needed for amanita mushroom, barbiturate, carbamazepine, valproic acid, phenytoin, meprobamate, theophylline, dapsone, and methotrexate. Urinary alkalinization also facilitates renal elimination of barbiturate.

- Hemoperfusion-related complications: hypocalcemia, charcoal embolization, leukopenia, thrombocytopenia, coagulopathy due to adsorption of coagulation factors

High-flux dialysis may improve solute removal, thus less need for hemoperfusion.

Hemofiltration alone may be considered for AG, desferrioxamine, sodium edetate, and theophylline toxicity.

Plasma exchange

- One to two plasma volume exchanges may be considered for rapid removal of toxins that exist predominantly in the plasma (V_d <1 L/kg).
- Agents removable by plasma exchange: amanita mushroom, digoxin, snake envenomation, cisplatin, natalizumab (used for the treatment of multiple sclerosis)

Molecular adsorbent recirculating system (MARS): This form of dialysis has an added albumin circuit to improve the removal of albumin-bound toxins. Not widely available.

COMMON POISONINGS THAT MAY REQUIRE EXTRACORPOREAL REMOVAL

Alcohols That May Require Extracorporeal Removal

Ethylene glycol, methanol (see Figure 2.1)

Significant ingestion of either ethylene glycol or methanol can give rise to high anion gap metabolic acidosis and high osmolal gap to greater than10 mOsm/kg.

Alkalinization to keep pH above 7.35

Correction of systemic acidosis limits the penetration of formic acid into end-organ tissues such as the retina by converting them into

formate, which cannot diffuse across cell membrane.

Fomepizole

- Fomepizole should be given to inhibit hepatic alcohol dehydrogenase in patients with blood levels of either alcohol above 20 mg/dL or serum osmolal gap above 20 mOsm/kg.
- Fomepizole should be continued until the alcohol level is below 20 mg/dL or below 1 mg/dL in the presence of end-organ damage.

Ethanol infusion

If fomepizole is not available, infuse 10% ethanol until the blood ethylene glycol or methanol level is undetectable.

Dialysis

HD if the alcohol level is above 50 mg/dL in the setting of severe metabolic acidosis or end-organ damage (eg, AKI or visual disturbances). Note that large surface area dialyzers (>1.5 m^2) should be used along with blood flow rate greater than 300 mL/min. Ethylene glycol and methanol levels should be monitored 2 hours postdialysis to assess for rebound. HD may be discontinued once the alcohol level is below 25 mg/dL.

Other supportive therapy

- In malnourished patients with ethylene glycol poisoning, add thiamine 100 mg and pyridoxine 5 mg IV to increase the metabolism of glyoxylate.
- In methanol poisoning, add folinic acid 50 mg IV q6h to increase metabolism of formic acid to CO_2 and H_2O.

Isopropyl alcohol (a.k.a. isopropanol, rubbing alcohol)

Clinical manifestations

- Isopropranolol intoxication is not as toxic as ethylene glycol or methanol and rarely fatal. Fomepizole or ethanol infusion is thus not necessary.
- Both isopropranolol and its metabolite acetone can cause CNS suppression, nausea/vomiting.

Laboratory findings

- Since isopropanol is metabolized to acetone (not an acid) by alcohol dehydrogenase, isopropanol ingestion does not cause a high anion gap metabolic acidosis. However, the acetone can be measured as positive "ketones" in either serum or urine. Low or absent serum ketones by the nitroprusside test after 2 hours from the time of ingestion in the absence of alcohol dehydrogenase inhibition (eg, concurrent ethanol ingestion or use of fomepizole) essentially rules out isopropanol ingestion.
- Increased serum osmolal gap reflects the presence of exogenous isopropanol molecules.

Management typically only requires routine supportive care, including IV fluid support and airway protection. For refractory and severe hemodynamic instability in association with very high levels greater than 500 mg/dL and osmolal gap greater than 100 mOsm/kg, HD may be considered.

Propylene glycol

Propylene glycol is commonly used as a solvent for IV formulations of lorazepam or diazepam. Although it is considered safe, large IV doses given over a short period of time can lead to propylene glycol toxicity.

Laboratory findings: osmolar gap greater than 10 mmol/L, anion gap acidosis (due to lactic acidosis), AKI, sepsis-like syndrome

Management: HD

Nonalcohol Drugs That May Require Extracorporeal Removal

β-Blocker overdose

- Activated charcoal should be administered to all patients presenting within 2 hours of β-blocker overdose.
- Supportive care with IV fluids for hypotension, atropine for severe bradycardia, β-agonist for bronchospasm, glucose for hypoglycemia

- Dialyzable β-blockers (hydrophilic, low protein binding): atenolol, metoprolol, acebutolol, nadolol
- Nondialyzable β-blockers: carvedilol, labetalol, propranolol, timolol
- There is evidence to suggest increased cardiovascular death in dialysis patients using dialyzable β-blockers compared to nondialyzable β-blockers.

Lithium overdose

Patients may present with hemodynamic instability, altered mental status, prolonged QT interval, arrhythmias, and/or kidney injury.
Signs and symptoms of lithium toxicity do not correlate well with lithium levels.
Lithium is highly dialyzable due to its LMW and low protein binding.
Indications for dialysis

- Lithium level greater than 3.5 to 4 mEq/L, or
- Lithium level greater than 2.5 mEq/L with CNS manifestation (altered mental status, seizures, coma), impaired renal excretion, or hemodynamic instability
- Between 2.5 and 3.5 mEq/L in asymptomatic patients with increasing levels or in patients with ESKD

NOTE

Rebound is a common problem following dialytic cessation because chronic Li accumulation in body compartments other than the intravascular volume can be released into the blood. Prolonged or continuous dialysis is recommended. Close postdialysis level monitoring (eg, q6h) is necessary.

Metformin-induced lactic acidosis in the setting of chronic use or acute overdose

Routine use recommendation: metformin use in patients with CKD (KDIGO guidelines): Its use is safe in patients with eGFR greater than 45 mL/min/1.73 m^2 unless the risk for AKI is high.

Reduce dose if eGFR less than 45 mL/min/1.73 m^2 and discontinue if eGFR less than 30 mL/min/1.73 m^2 (contraindicated).

For metformin overdose:

- Provide supportive care and alkalinization with sodium bicarbonate to maintain pH above 7.15 until the acute toxicity resolves.
- Metformin is dialyzable. However, the beneficial effect of HD in metformin-induced lactic acidosis lies more in correcting the acidosis rather than removing metformin.
- HD is recommended if any of the following is present:
  - Lactate level greater than 20 mmol/L
  - Severe metabolic acidosis (pH ≤7.0) or
  - Medical treatment failure (as determined by pH, lactate levels, or clinical status within 2-4 hours) despite appropriate supportive care and bicarbonate therapy
- HD may be considered if any of the following is present (limited evidence):
  - Lactate levels between 15 and 20 mmol/L
  - Metabolic acidosis (pH 7.0-7.1)
  - Presence of comorbidities (eg, shock, kidney injury, liver failure, or decreased level of consciousness). Kidney injury is defined as creatinine greater than 2 mg/dL (adults) or greater than 1.5 mg/dL (older adults), eGFR less than 45 mL/min/1.73 m^2, oliguria, or anuria. Liver failure is defined as liver injury with coagulopathy (INR >1.5) and any degree of encephalopathy.

Digitalis toxicity

Clinical manifestations:

- CNS symptoms ranging from drowsiness, lethargy, to hallucinations, seizures, visual disturbances with classic yellow halos around lights, nonspecific GI symptoms, cardiac arrhythmias

- Electrolytes: hyperkalemia in acute toxicity; hypokalemia, and hypomagnesemia in chronic toxicity

Toxicity risks: advanced age, hypothyroidism, kidney injury, hypo- or hyperthyroidism, alkalosis or acidosis, myocardial disease, ischemia or infarction, hypoxemia, electrolyte abnormalities (hypo- or hyperkalemia, hypercalcemia, hypomagnesemia, hypernatremia)

Supportive care

- Routine supportive care, fluids, airway protection, drug discontinuation
- Activated charcoal in acute overdose or accidental ingestion
- Cholestyramine may bind enterohepatically recycled digoxin in acute overdose.
- Hyperkalemia: insulin plus glucose, sodium bicarbonate if metabolic acidosis
- Concurrent hypokalemia and hypomagnesemia: supplement as needed

Indication for digoxin immune Fab (Digibind)

- Life-threatening dysrhythmias
- Acute ingestion dose greater than 10 ng/mL in acute ingestions or greater than 6 ng/mL in chromic ingestion
- Hyperkalemia greater than 5 mEq/L
- Altered mental status
- Rapid clinical deterioration

Other extracorporeal removal options

- Digoxin is not dialyzable. However, dialysis is indicated for hyperkalemia and kidney failure. Digibind is also minimally dialyzable.
- If Digibind is not available or contraindicated, hemoperfusion should be considered.

Salicylate (aspirin) intoxication

Clinical manifestations

- Initial presentation may be respiratory alkalosis alone due to activation of respiratory center, followed by high anion gap metabolic acidosis due to accumulation of lactic acids and ketoacids.
- Other characteristic manifestations: fevers, tinnitus, vertigo, blurry vision

Management

- Gastric lavage should be considered within 12 hours of ingestion if airway is protected.
- Urinary alkalinization to keep urine pH greater than 7.5 in nonoliguric patients to increase the levels of ionized salicylates ($NaHCO_3$ 1-2 mEq/kg bolus followed by infusion [100-150 mL/h] of 100-150 mEq mixed in 1 L of 5% dextrose). Ionized salicylates are more easily renally excreted and less likely to penetrate and accumulate in tissue than the nonionized form. It is important to note that acidemia increases salicylate CNS toxicity.
- Glucose supplementation to avoid CNS hypoglycemia, which may occur despite serum normoglycemia

Indications for HD: serum levels greater than 90 to 100 mg/dL or lower if presence of AKI, marked acidemia, noncardiogenic pulmonary edema, or neurologic involvement (altered mental status, hyperthermia, seizure)

Theophylline

- Theophylline is highly dialyzable due to its low V_d and protein binding.
- High-efficiency HD is more effective than hemoperfusion in theophylline removal.
- Combining HD with hemoperfusion may enhance Cl and prevent saturation of hemoperfusion cartridge

HD indications for **acute intoxication**

- Severe symptoms such as shock, seizure, or life-threatening arrhythmias

- Serum level 100 mg/L or higher, regardless of symptoms
- Clinical deterioration despite optimal supportive care and multiple-dose activated charcoal
- Rising theophylline levels despite optimal supportive care and multiple-dose activated charcoal
- If the initial level is 80 mg/L or above, then one additional rising level measured 2 hours later.
- If the initial level is less than 80 mg/L, then a subsequent level that rises above 80 mg/L.
- In patients in whom administration of activated charcoal is not possible (eg, protracted vomiting, altered mental status)
- HD may be beneficial in patients at increased risk for seizure (eg, history of seizure, concomitant use of medications that lower seizure threshold) or in those with a history of arrhythmias.

HD indications for **chronic intoxication**

- Severe symptoms such as shock, seizure, or life-threatening arrhythmias
- Serum level 60 mg/L or above, regardless of symptoms
- Serum levels greater than 40 to 50 mg/L in patients older than 60 to 65 years of age

CHAPTER 11

Acute Kidney Injury/Intensive Care Unit (ICU) Nephrology

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ACUTE KIDNEY INJURY (AKI)

Epidemiology and Clinical Impact of AKI

- AKI occurs in approximately 20% of hospitalized patients and up to 50% of patients admitted to the intensive care unit (ICU).
- AKI increases the risk for chronic kidney disease (CKD) progression and de novo CKD in patients with and without underlying CKD, respectively.
- AKI is associated with higher rates of cardiovascular (CV) events (heart failure, acute myocardial infarction) and CV mortality.
- In patients with diabetes mellitus type 2, any AKI episode independently increases the risk for the development of stage 4 CKD. The adverse impact of AKI on the development of CKD is similar to that seen with proteinuria.

Classification of AKI and Acute Kidney Disease/Disorder (AKD)

The diagnosis and staging of AKI previously defined by various organizations are summarized in **Appendix A11.1**: **R**isk, **I**njury, **F**ailure, **L**oss of kidney function, **ESKD** (end-stage kidney disease; RIFLE), Acute Kidney Injury Network (AKIN), Kidney Disease: Improving Global Outcomes (KDIGO). Consensus on the exact criteria for AKI is still needed.

Definition of AKI

- Increase in SCr by 0.3 mg/dL or more within 48 hours, or
- Increase in serum creatinine (SCr) by greater than 50% within 7 days, or
- Oliguria

Definition of AKD

Conditions of impaired kidney function not meeting criteria (in terms of severity and/or duration of kidney damage) for either AKI or CKD but with associated adverse outcomes requiring clinical care

Early Identification of AKI

A rise in SCr is a late indication of AKI. Earlier detection of AKI is thought to improve outcomes.

Selected biomarkers for the early detection of AKI (see **Table 11.1**).

Table 11.1 Selected biomarkers that have been studied in the setting of AKI

Biomarkers	Comments
Liver-type fatty acid-binding protein	• Detected within 1 h, peaks within 6 h

Biomarkers	Comments
(L-FABP)	• Involves in fatty acid transport • Protects against oxidative stress injury
Neutrophil gelatinase–associated lipocalin (NGAL)	• Detected at 3 h, peaks at 6 h with sustained elevation up to 5 d • Functions as chelator of labile iron released from damaged tubules • Upregulates the renoprotective enzyme heme-oxygenase-1 • NGAL level may be affected by systemic infections, inflammatory conditions, anemia, hypoxia, and malignancies.
Interleukin-18 (IL-18)	• Detected within 6 h, peaks at 12-18 h • Upregulated in AKI • Proinflammatory
Kidney injury molecule-1 (KIM-1)	• Detected within 6 h, peaks at 48-72 h • Activates immune cells and promotes apoptotic and necrotic cell clearance and remodeling of injured epithelia
Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein (TIMP-2*IGFBP7)	• Detected within 12 h • Induces transient cell cycle arrest in face of injury
Cystatin C (Cyst C)	• Cysteine protease inhibitor • Detected at 12-24 h, peaks at 24-48 h • Note: Albuminuria ↑ urinary Cyst C due to competitive proximal tubular endocytosis of albumin.

The ideal biomarker is expected to have an early increase in level with AKI, correlate with AKI course and severity, and be clear with AKI recovery.

Abbreviation: AKI, acute kidney injury.

Neutrophil gelatinase–associated lipocalin (NGAL): NGAL is predominantly detected in proximal tubular cells undergoing mitosis and expressing proliferating cell nuclear antigen. In healthy individuals, urine and plasma NGAL levels are low but increase significantly with ischemic or nephrotoxic kidney injury.

Kidney injury molecule 1 (KIM-1): a transmembrane glycoprotein that is undetectable in normal kidney tissue or urine but is expressed at high levels in dedifferentiated proximal tubular cells after ischemic or toxic injury and in renal cell carcinoma

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and tissue insulin-like growth factor binding protein 7 (IGFBP7):

- TIMP-2 and IGFBP7 function as both autocrine and paracrine signals to arrest cell cycle and shut down cell function with early kidney injury.
- Urinary levels of both TIMP-2 and IGFBP7 are increased in early kidney injury.
- Early optimized kidney care or prompt nephrology consultation based on elevated TIMP-2*IGFBP7 values has been shown to reduce the severity of AKI.
- The use of urinary TIMP-2*IGFBP7 in patients undergoing cardiopulmonary bypass (CPB) as a screening tool in patients at high risk for AKI has been shown to reduce the prevalence of severe AKI when implemented as part of AKI bundle care.

Electronic alerts (E-alerts)

- Direct automated data analysis from electronic health care records may be used to alert providers of patients with early AKI or at risk for AKI.
- Alerts can be used to provide early AKI bundle care and reduction or avoidance of nephrotoxic medications to improve renal outcomes.

AKI Bundle Care

- KDIGO proposed "bundle care" for the prevention of AKI.
- Bundle care includes optimization of volume status and perfusion pressure, consideration of invasive hemodynamic monitoring, avoidance of hyperglycemia and nephrotoxic agents, consideration of alternatives to intravenous radiocontrast agents, and close monitoring of SCr and urine output (UO).

AKI Risk Stratification and Prognostication

Multiple AKI risk stratification and prognostication scoring systems based on patients' baseline characteristics and kidney function, clinical context, and early signs of kidney injury have been developed in recent years.

Renal functional reserve testing (RFR)

- RFR is defined as the increase in glomerular filtration rate (GFR) following protein loading.
- An increase in GFR of less than 15 mL/min/1.73 m^2 3 hours following a protein load of 1.2 g/kg body weight has been suggested to predict an 11.8-fold increase in postoperative risk for AKI among patients undergoing elective cardiac surgery. An RFR in healthy individuals is approximately 30 mL/min/1.73 m^2.

Furosemide stress test (FST)

FST may be used in patients with euvolemia to hypervolemia with AKI to predict the risk for severe AKI and the need for kidney replacement therapy (KRT).

FYI

FST protocol

- Infuse 1.0 to 1.5 mg/kg of furosemide (the former dose is for furosemide naïve individuals and the latter is for individuals with prior exposure).
- UO of less than 200 mL within 2 hours in patients with stage 1 AKI predicts risk of progression to stage 3 AKI and need for KRT. In the kidney transplant recipient, poor FST response predicts delayed graft function.

Renal angina index (RAI): RAI is a validated scoring tool used to predict AKI.

FYI

Renal angina index = AKI risk condition score × kidney injury score

- AKI risk conditions (assigned score): trauma/sepsis (1), nephrotoxic drugs/burn injuries (3), ventilation/cardiac surgery (5)
- Kidney injury (assigned score): No change in SCr (1), 0% to 24% (2), 25% to 49% (3), 50% or more increase in SCr (8)
- RAI score interpretation: RAI of 8 or more (out of 40 maximum score) suggests greater predictability of AKI.

Proteinuria: Preexisting proteinuria (albuminuria) predicts AKI risk, AKI requiring KRT, unfavorable prognosis for renal recovery in those who develop AKI requiring KRT, and prolonged hospital stay.

Mechanisms of AKI

Ischemia-related acute tubular necrosis (ATN):

Proximal and distal tubules may be affected in a patchy distribution.

Functional changes:

- Loss of tubular cell polarization, that is, loss of differentiation between apical and basolateral sides, leading to reabsorption of urine instead of urine excretion aka "urine backleak"
- Microvascular injury, vascular congestion, intraglomerular vasoconstriction

Histopathology (**Figure 11.1**)

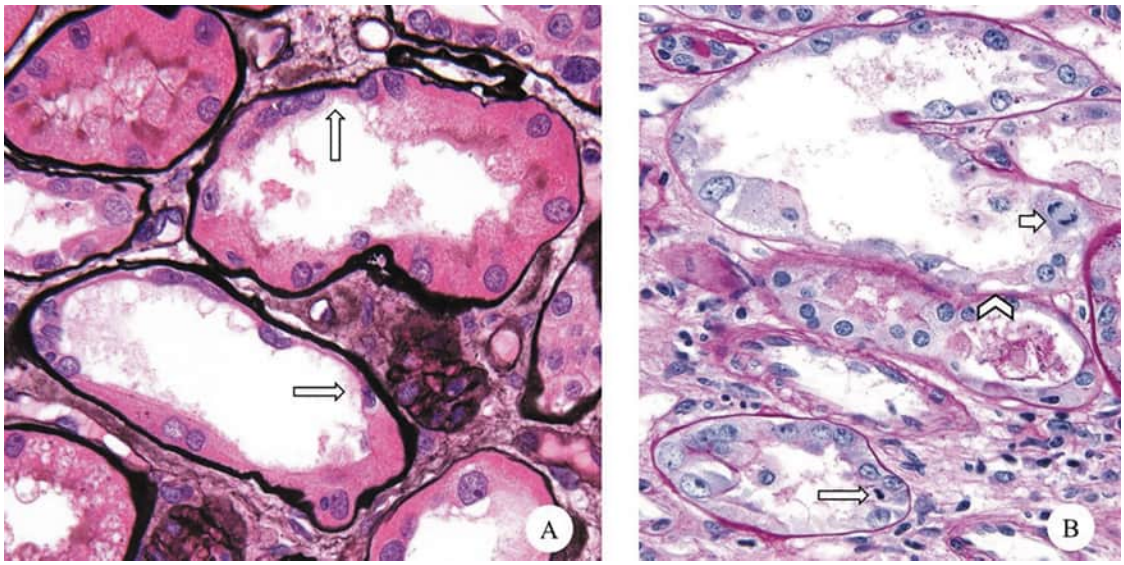


FIGURE 11.1 **Acute tubular necrosis.** Acute tubular cell injury and necrosis in proximal tubules. A. There is acute tubular injury with loss of the microvillus brush border and cell cytoplasm with epithelial cell flattening (arrows) and relative dilatation of the tubular lumens (Jones silver × 400). B. In addition to tubular cell loss of brush borders and cytoplasm, there are tubular cell necrosis (long arrow), a mitotic figure (short arrow) reflecting regeneration and repair, and epithelial cell detachment with a focus of denuded tubular basement membrane (arrowhead) (periodic acid methenamine silver × 400).

- Proximal tubular cell irregular vacuolization and attenuation of the cytoplasm and loss of brush border, often with disruption and sloughing of epithelial cells from the tubular basement membrane forming intratubular epithelial cell casts
- Apoptosis of proximal tubular cells
- Necrosis of tubular cells is typically seen in relatively few cells.

Nephrotoxin-related AKI

Nephrotoxin-related AKI typically involves proximal tubular cells.

Mechanisms of action are drug specific and may include alterations in intraglomerular hemodynamics, direct tubular cytotoxic effects with generation of local inflammatory response and reactive oxygen species, local or systemic drug-allergic response, systemic endothelial injury with associated immunologic and nonimmunologic responses, or drug-crystallization with microtubular obstruction.

Recreational drug-related AKI

- Cocaine (rhabdomyolysis, severe renal vasoconstriction with possible renal infarction, levamisole-laced cocaine with associated antineutrophil cytoplasmic antibodies [ANCA]-vasculitis)
- Oxymorphone (Opana): thrombotic microangiopathy (TMA), rhabdomyolysis
- Methamphetamines, ecstasy (rhabdomyolysis, acute tubulointerstitial nephritis [ATIN]), ATN, hyponatremia, malignant hypertension [HTN]

- Synthetic cannabinoids (ATN, ATIN, mild elevation of creatine phosphokinase [CPK], rare reports of rhabdomyolysis, or oxalate nephropathy)
- Heroin (heroin crystal nephropathy, rhabdomyolysis, amyloidosis, nephrotic syndrome)
- Bath salts—synthetic cathinones (rhabdomyolysis, hyperuricemia)
- Ketamine—*N*-methyl-D-aspartate (NMDA) receptor antagonist (lower urinary tract dysfunction, obstructive uropathy, rhabdomyolysis

Medication-related AKI (See Chapter 10: Pharmacology)

Sepsis-related AKI:

- Activation of the innate immune system in response to an inciting pathogen leads to increased oxidative stress, procoagulant state, endothelial injury, and recruitment of inflammatory cells, all acting in concert to promote and exacerbate the underlying AKI.
- The septic/shock state is also associated with increased glomerular blood flow due to dilatation of both afferent and efferent arterioles. However, net glomerular filtration pressure is reduced because there is greater efferent vasodilation than afferent vasodilation. The reduced GFR may partially contribute to sepsis-related AKI.

Routine Diagnostic Tools for Diagnosing AKI

Microscopic examination of urinary sediment

Evaluation of cells, cellular casts

- Hyaline casts:
  - Predominantly made up of Tamm-Horsfall protein, aka uromodulin protein
  - Indicate reduced renal perfusion (See **Figure 11.2** for causes of renal hypoperfusion.)

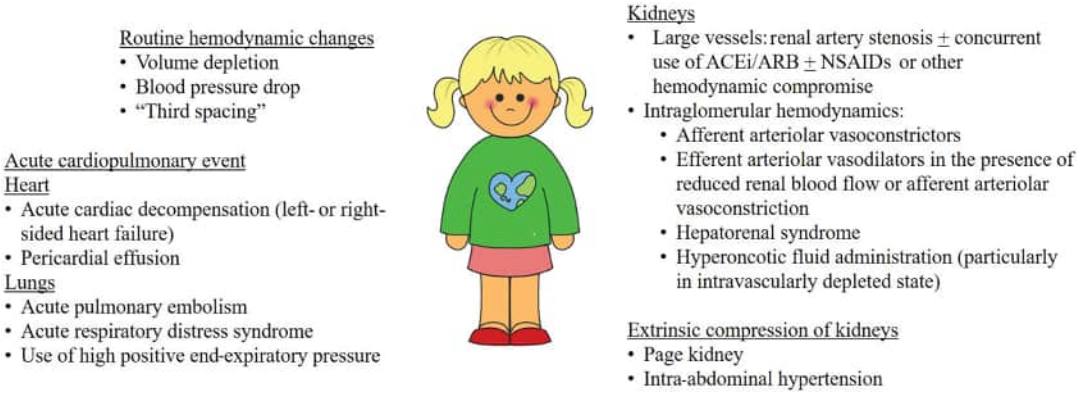

Routine hemodynamic changes
• Volume depletion
• Blood pressure drop
• "Third spacing"
Acute cardiopulmonary event
Heart
• Acute cardiac decompensation (left- or right-sided heart failure)
• Pericardial effusion
Lungs
• Acute pulmonary embolism
• Acute respiratory distress syndrome
• Use of high positive end-expiratory pressure
Kidneys
• Large vessels: renal artery stenosis ± concurrent use of ACEi/ARB ± NSAIDs or other hemodynamic compromise
• Intraglomerular hemodynamics:
• Afferent arteriolar vasoconstrictors
• Efferent arteriolar vasodilators in the presence of reduced renal blood flow or afferent arteriolar vasoconstriction
• Hepatorenal syndrome
• Hyperoncotic fluid administration (particularly in intravascularly depleted state)
Extrinsic compression of kidneys
• Page kidney
• Intra-abdominal hypertension

FIGURE 11.2 Differential diagnoses of hemodynamic acute kidney injury categorized by organ system. Renal hypoperfusion leading to AKI can be caused by any condition that can reduce blood flow in the kidneys.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

- Red blood cell (RBC) casts: acute glomerulonephritis (GN) until proven otherwise
- White blood cell (WBC) casts: pyelonephritis or tubulointerstitial nephritis
- Granular casts: nonspecific, indicates the presence of cells that have degenerated
- Broadcasts: chronic low urine flow
- Muddy brown casts: ATN

- Waxy casts: degraded cellular casts seen in CKD with poor urine flow

Crystalluria

- Consider drug-induced crystals (see **Chapter 6: Tubular, Interstitial, and Cystic Disorders**).
- High amount of uric acid crystals may be observed with tumor lysis syndrome.

Urine eosinophils

- Poor sensitivity and specificity in the diagnosis of AIN
- No longer recommended in the evaluation of AIN

Urine volume

- Anuria is more likely seen with complete urinary obstruction, vascular catastrophe, bilateral renal cortical necrosis, severe ATN, or severe rapidly progressive GN.
- Oliguric AKI, defined as having UO of less than 500 mL/d, is associated with worse outcome than nonoliguric AKI.

Fractional excretion of sodium (FeNa) and fractional excretion of urea (FeUrea)

- FeUrea versus FeNa: FeUrea is typically used in patients receiving diuretics because urea reabsorption occurs primarily in the proximal tubules and is less affected by loop and thiazide diuretics. In contrast, Na^+ excretion, hence FeNa, can be elevated with diuretic use even in the prerenal state.
- In nonoliguric AKI, FeNa of less than 1% or FeUrea of 35% or less generally indicates prerenal AKI.

NOTE

- FeNa may also be less than 1% in patients with sepsis, hemoglobinuria, myoglobinuria, radiocontrast exposure, heart failure, and advanced cirrhosis due to severe renovasoconstriction.
- In patients with cirrhosis, FeNa of less than 0.1 may be consistent with hepatorenal syndrome, FeNa greater than 0.3 is associated with ATN, and FeNa of 0.1 to 0.3 may be indicative of prerenal AKI.

Kidney/bladder ultrasound

- Kidney size is generally normal to enlarged with AKI. However, enlarged kidneys may be seen in advanced subacute/chronic diabetic kidney disease, infiltrative disease, amyloidosis, HIV-infected related nephropathy, presence of large cysts, or hydronephrosis.
- Bladder ultrasound may be obtained to measure post-void residual volume in at-risk individuals (eg, enlarged prostate, neurogenic bladder [associated with diabetes mellitus, neurologic complications, or drug induced], AKI post-traumatic Foley insertion).

Hemodynamic (Prerenal) AKI

AKI may be caused by any condition that reduces or impedes normal blood flow to the kidneys (see **Figure 11.2**). Common hemodynamic causes of AKI are discussed later.

Rapid fall in baseline blood pressure (BP) (eg, overly rapid treatment of HTN, acute volume loss)

Volume depletion/reduced effective circulating volume

- True volume depletion: bodily fluid loss, no access to adequate fluid intake
- Reduced effective circulating volume: heart failure, cirrhosis, nephrotic syndrome

"Third spacing" (eg, sepsis, acute pancreatitis, muscle trauma)

Cardiorenal syndrome (CRS)

Pathologic disorder of the heart and kidneys, in which acute or chronic dysfunction of one organ induces acute or chronic dysfunction of the other.

CRS type 1, acute CRS: Abrupt worsening of cardiac function (eg, acute pulmonary embolism, myocardial infarction, valvular rupture, rapid accumulation of pericardial effusion) leads to AKI.

CRS type 2, chronic CRS: Chronic abnormalities in cardiac function lead to progressive CKD.

CRS type 3, acute renocardiac syndrome: AKI leads to acute cardiac dysfunction.

CRS type 4, chronic renocardiac syndrome: CKD leads to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse CV events.

CRS type 5, secondary CRS: Systemic condition (eg, sepsis) leads to both cardiac and renal dysfunction. Mechanisms of AKI are thought to result from inflammatory mediators, cytokine-mediated nitric oxide production and associated vasodilatory state and shock, endothelial dysfunction leading to thrombotic complications, capillary leakage syndrome leading to intravascular volume depletion, and interstitial edema leading to reduced perfusion pressure to tubular cells.

Risk factors for CRS: older age, female gender, baseline CKD, Caucasian American race, diastolic heart failure, history of heart failure, diabetes mellitus, spontaneous bacterial peritonitis (SBP) of greater than 160 mm Hg

Pathophysiology of CRS

- Reduced cardiac output leads to renal hypoperfusion.
- Reduced cardiac output with associated venous congestion or severe right ventricular dysfunction leads to increased renal venous pressure and renal resistance, thereby impairing intrarenal blood flow. Optimal renal perfusion depends on a balance between mean arterial pressure (MAP) and renal venous pressure.
- Endothelial stretch from peripheral venous congestion leads to a vascular endothelial proinflammatory state.
- Neurohormonal activation involving the sympathetic nervous system, renin-angiotensin-aldosterone system, and nonosmotic vasopressin release leads to systemic vasoconstriction and enhanced renal Na^+ and H_2O excretion.

Management

- Optimization of cardiac function per underlying etiology
- For patients presenting with evidence of intravascular congestion (ie, HTN, orthopnea, third heart sound S3, jugular vein pulsation >8 cm, inferior vena cava [IVC] collapsibility <50%), adding a vasodilator can be beneficial.
- For patients presenting with tissue edema (ie, peripheral pitting edema, rales, pleural effusion, interstitial alveolar edema, lung ultrasonography revealing >15 B-lines when scanning 28 sites, hepatomegaly, ascites), diuresis is indicated.
- Strategies for optimal diuresis:
  - Start with intravenous furosemide 40 mg or equivalent for patients not currently on loop diuretic; for those currently on home loop diuretic, double home dose.
  - If after 6 hours, UO is greater than 100 to 150 mL/h, administer the initial dose every 12 hours.
  - If UO is less than 100 mL/h, double diuretic dose, and reassess UO every 6 hours and titrate to achieve a goal, not to exceed a single furosemide dose of 150 mg or total dose of 600 mg daily.

- If after the first 24 hours, UO exceeds 3 L, consider dividing total dose from day before q6h. If UO exceeds 5 L, reduce diuretic dose.
- Add-on diuretic options for edematous state refractory to high-dose loop diuretics: thiazide/thiazide-like diuretic, amiloride, mineralocorticoid receptor antagonists, carbonic anhydrase inhibitor acetazolamide, and/or sodium-glucose cotransporter-2 inhibitor (SGLT2i)

> **NOTE**
>
> AKI during decongestive therapy with diuretics should be fully evaluated and not assumed to be due to diuresis. In some instances, the observed AKI may reflect ATN that had already started before admission when patients initially developed acute decompensated heart failure, and the continuing rise in SCr upon admission only reflects the natural course of the ATN already in progress. Therefore, discontinuation of diuretics due to AKI in obviously congested patients may be unwarranted.

Extracorporeal ultrafiltration (UF)

- May be considered in patients with poor response or refractory to medical management
- In patients on peritoneal dialysis (PD), the use of icodextrin-based solutions may be more advantageous compared with dextrose-based solutions because icodextrin does not activate peritoneal aquaporins for water removal, but instead, concurrent water and sodium transport occur via intercellular pores, thereby potentially enhancing the removal of total body sodium.
- Optimal UF rate has not been established but likely needs to be individualized.

Renovascular compromise (eg, acute obstruction of renal artery [eg, aortic dissection extending into renal artery, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) in severe bilateral renal artery stenosis])

Intraglomerular hemodynamic compromise

- Predominant afferent vasoconstrictors: nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, calcineurin inhibitors (CNI), amphotericin, radiocontrast agents
- Predominant efferent vasodilators in patients with suboptimal baseline glomerular filtration: ACEi/ARB

Hepatorenal syndrome (HRS)-AKI

See **Chapter 1: Sodium and Water Abnormalities** for definition, pathogenesis, and management of HRS.

HRS-AKI is a diagnosis of exclusion.

- Routine evaluation for causes of AKI other than HRS must be performed.
- Etiologies relevant to patients with cirrhosis include intra-abdominal hypertension (IAH) (tense ascites with or without peritonitis), concurrent infections or nephrotoxins leading to both kidney and liver failure, and pigmented cast nephropathy (particularly in cases with total bilirubin level >20 mg/dL).
- Infusion of hyperoncotic albumin in patients with cirrhosis who are volume depleted and do not have peripheral edema can reduce net peritubular capillary perfusion pressure and may precipitate ATN.

Management of HRS (**Table 11.2**)

Table 11.2 Hepatorenal syndrome: preventive and management strategies

Category	Specific therapies	Comments
Hepatorenal syndrome (HRS) prevention in the setting of SBP	Prophylactic antibiotic for SBP in at-risk individuals	*Short-term prophylactic therapy:* • *Patients hospitalized for gastrointestinal bleed (ceftriaxone 1 g/d); transition to oral quinolone or trimethoprim-sulfamethoxazole bid × 7 d after stabilization* • *Patients hospitalized for other reasons with ascitic total protein <1 g/dL* *Prolonged prophylactic therapy: (quinolone or trimethoprim-sulfamethoxazole DS daily):* • *Patients with ≥1 episode of SBP* • *Patients with cirrhosis & ascitic fluid total protein <10 g/L with Child-Pugh Score >9, serum bilirubin >3 mg/dL, serum creatinine >1.2 mg/dL, blood urea nitrogen (BUN) >20 mg/dL, or S[Na^+] <130 mmol/L*
	Albumin infusion in patients who present with SBP	Administer 25% albumin at 1.5 g/kg at diagnosis and 1 g/kg IV 48 h later at diagnosis of SBP.
Optimization of hepatic venous blood return to central circulation	Transjugular intrahepatic portosystemic shunt (TIPS)	TIPS is not well tolerated in patients with end-stage liver failure (Child-Pugh class C) due to high risk for complications.
Treatment of HRS	Systemic/splanchnic vasopressors + albumin • Terlipressin • Norepinephrine • Vasopressin • Midodrine + octreotide	Most effective options are terlipressin + albumin or norepinephrine + albumin.
	Renal vasodilator: serelaxin	More data needed
Removal of albumin-bound toxins	Albumin dialysis	No survival benefit established
Liver cure	Liver transplant	Only cure

Abbreviations: DS, double strength; IV, intravenous; SBP, spontaneous bacterial peritonitis.

See also **Chapter 1: Sodium and Water Abnormalities** for a more detailed discussion on the management of HRS and **Appendix A1.3** for drug dosing.

- Preventive strategies:
  - Avoidance of nephrotoxins, NSAIDs, and overly aggressive diuresis
  - Use of hyperoncotic albumin in patients who present with or are at high risk for SPB
  - Placement of transjugular intrahepatic shunt (TIPS) to improve central venous return from portal vein
- Combined use of daily albumin infusions and vasoconstrictors may potentially reverse HRS-AKI.
  - Vasoconstrictors that may be used include terlipressin, norepinephrine, vasopressin, and midodrine + octreotide combination.
  - Compared with placebo, terlipressin was shown to be more effective in reversing HRS but without improving 90-day survival benefit (CONFIRM [Confirming the Effect of Terlipressin on Mortality in Patients with Hepatorenal Syndrome] study).
  - Norepinephrine and terlipressin may be comparable in terms of efficacy. However, norepinephrine requires a continuous infusion while terlipressin can be given as intermittent injections.
  - Octreotide (splanchnic vasoconstrictor) and midodrine (systemic vasoconstrictor) combination is not as effective as terlipressin.

    - Of note, terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or acute-on-chronic liver failure Grade 3 are at increased risk. The use of terlipressin is contraindicated in patients with hypoxia or worsening respiratory symptoms.
    - Due to potential ischemic complications, vasoconstrictors should not be used in patients with ischemic heart disease or peripheral vascular disease.
- Large-volume paracentesis may be considered in patients with tense ascites to reduce intra-abdominal pressure (IAP), thereby improving renal perfusion.
- AKI due to renal hypoperfusion in patients with cirrhosis who are volume depleted and do not have peripheral edema should be treated with crystalloids, not hyperoncotic albumin.
- Use of renal vasodilator: Serelaxin is a recombinant form of the human peptide hormone relaxin-2, that has been studied for potentially improving renal blood flow and portal venous blood flow. Data are lacking.
- Molecular adsorbent recycling system (MARS), fractionated plasma separation and adsorption (Prometheus), and single-pass albumin dialysis systems are systems that use an albumin circuit to compete for protein-bound toxins not metabolized by the diseased liver. Current data suggest improvement in hepatic encephalopathy and reduction of bilirubin level but not survival.
- Currently, liver transplantation is the only cure. The incidence of ESKD following liver transplantation is 7% in patients with HRS versus 2% in those without HRS.

IAH leading to abdominal compartment syndrome (ACS)

- IAH is defined as having sustained IAP 12 mm Hg or more. IAP is measured at end-expiration in the supine position after ensuring the absence of abdominal muscle contractions, with transducer zeroed at the level of midaxillary line.
- ACS is defined as having a sustained IAP of 20 mm Hg or higher along with or without abdominal perfusion pressure (APP) of less than 60 mm Hg that is associated with new organ dysfunction/failure, where APP is defined as: APP = MAP − IAP, where MAP is mean arterial pressure.

Risks for IAH/ACS

- Diminished abdominal wall compliance: abdominal surgery, major trauma/burns, prone positioning
- Increased intraluminal contents: gastroparesis/gastric distention/ileus, ileus, colonic pseudo-obstruction, volvulus
- Increased intra-abdominal contents: acute pancreatitis, distended abdomen, hemo-/pneumoperitoneum or intraperitoneal fluid collections, intra-abdominal or retroperitoneal tumors, laparoscopy with excessive insufflation pressures, liver dysfunction/cirrhosis with ascites, PD
- Capillary leak/fluid resuscitation: acidosis, hypothermia, massive positive fluid balance
- Others: age, bacteremia, coagulopathy, increased head of bed angle, massive incisional hernia repair, mechanical ventilation, obesity or increased body mass index, positive end-expiratory pressure (PEEP) of greater than 10 mm Hg, peritonitis, pneumonia, sepsis, shock, or hypotension

Management of IAH/ACS: If IAP is 12 mm Hg or higher, begin medical therapy to reduce IAP:

- Measure IAP every 4 to 6 hours or more. Titrate therapy to maintain IAP at 15 mm Hg or less.
- Therapeutic measures to reduce IAP:
    - Evacuate intraluminal contents: nasogastric and/or rectal tube, initiate gastro-/colo-prokinetic agents, minimize or discontinue enteral nutrition, lower bowel decompression with enemas or even colonoscopy as needed.

- Evacuate intra-abdominal space-occupying lesions or fluids as applicable (eg, large-volume paracentesis if safely tolerated). Patients without peripheral edema are at increased risk for circulatory collapse and AKI with large-volume paracentesis.
- Improve abdominal wall compliance: Ensure adequate sedation and analgesia: Remove constrictive dressings, consider reverse Trendelenburg position with or without neuromuscular blockade.
- Minimize fluid administration, remove excess fluids with the use of diuretics or even UF if necessary.
- Optimize systemic/regional perfusion.
- If IAP is higher than 20 mm Hg and new organ dysfunction/failure occurs despite maximal medical intervention, consider surgical abdominal decompression.

Clinical manifestations of IAH/ACS

- Increased IAP with typically (but not always) tense abdomen
- Increased peak inspiratory pressure, decreased tidal volume (due to abdominal compartment encroaching into thoracic cavity)
- Increased central venous pressure (CVP), pulmonary arterial wedge pressure
- Reduced cardiac index (blood pumped against high-pressured abdominal cavity)
- Oliguria (reduced blood flow in renal vein and direct cortical pressure)

Page kidney

- Results from external compression of kidney (eg, perinephric subcapsular hematoma, lymphocele around transplanted kidney, large simple cyst, retroperitoneal compression)
- Compression of intrarenal vessels leads to renal hypoperfusion, ischemia, activation of the renin-angiotensin-aldosterone system, and associated HTN.
- Treatment: decompression of underlying cause

Hyperoncotic AKI

- This is seen with the rapid infusion of a large quantity of osmotically active substances such as mannitol, dextran, or albumin.
- Histopathology: proximal tubules with cytoplasmic isometric vacuoles
- When glomerular oncotic pressure far exceeds glomerular hydrostatic pressure, there is a net reduction in glomerular filtration (**Figure 11.3**).
- Similarly, when the oncotic pressure within peritubular capillaries is rapidly increased with the infusion of hyperoncotic albumin in patients with existing low intracapillary hydraulic pressure (ie, intravascular depletion), the peritubular capillary perfusion pressure that is necessary to supply nutrients and oxygen to renal tubules is also reduced, thereby causing tubular ischemia and AKI.

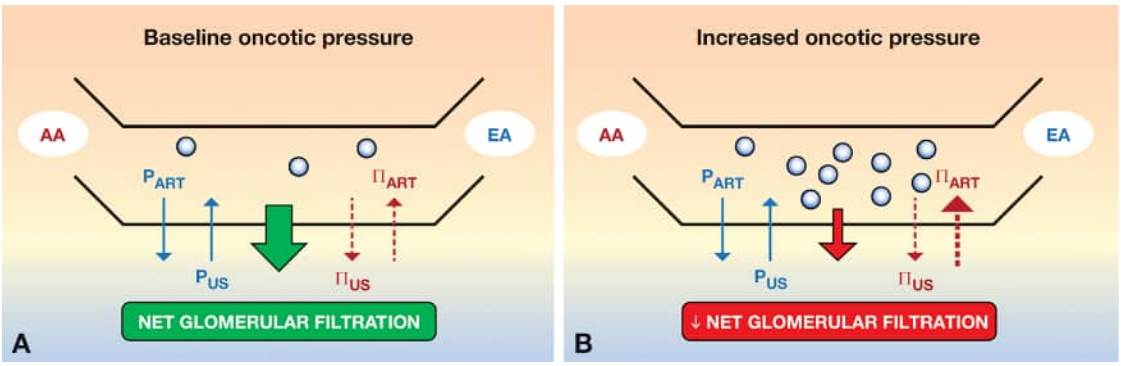


FIGURE 11.3 Reduction in net glomerular filtration with rapid increase in intra-arteriolar oncotic pressure. The lower intra-arteriolar oncotic pressure in panel A provides a greater net glomerular filtration compared with panel B where the higher oncotic pressure drives the force of filtration into the intra-arteriolar space. Abbreviations: AA, afferent arteriole; EA, efferent arteriole; P_{ART}, arteriolar hydraulic pressure; P_{US}, urinary space hydraulic pressure; π_{ART}, arteriolar oncotic pressure; π_{US}, urinary space oncotic pressure.

Vascular Causes of AKI

Thromboembolic disease

- Microangiopathy and hemolytic anemia (MAHA), thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP/HUS), antiphospholipid syndrome, scleroderma, malignant HTN
- Systemic embolism (eg, spontaneous bacterial endocarditis)

Atheroembolic disease

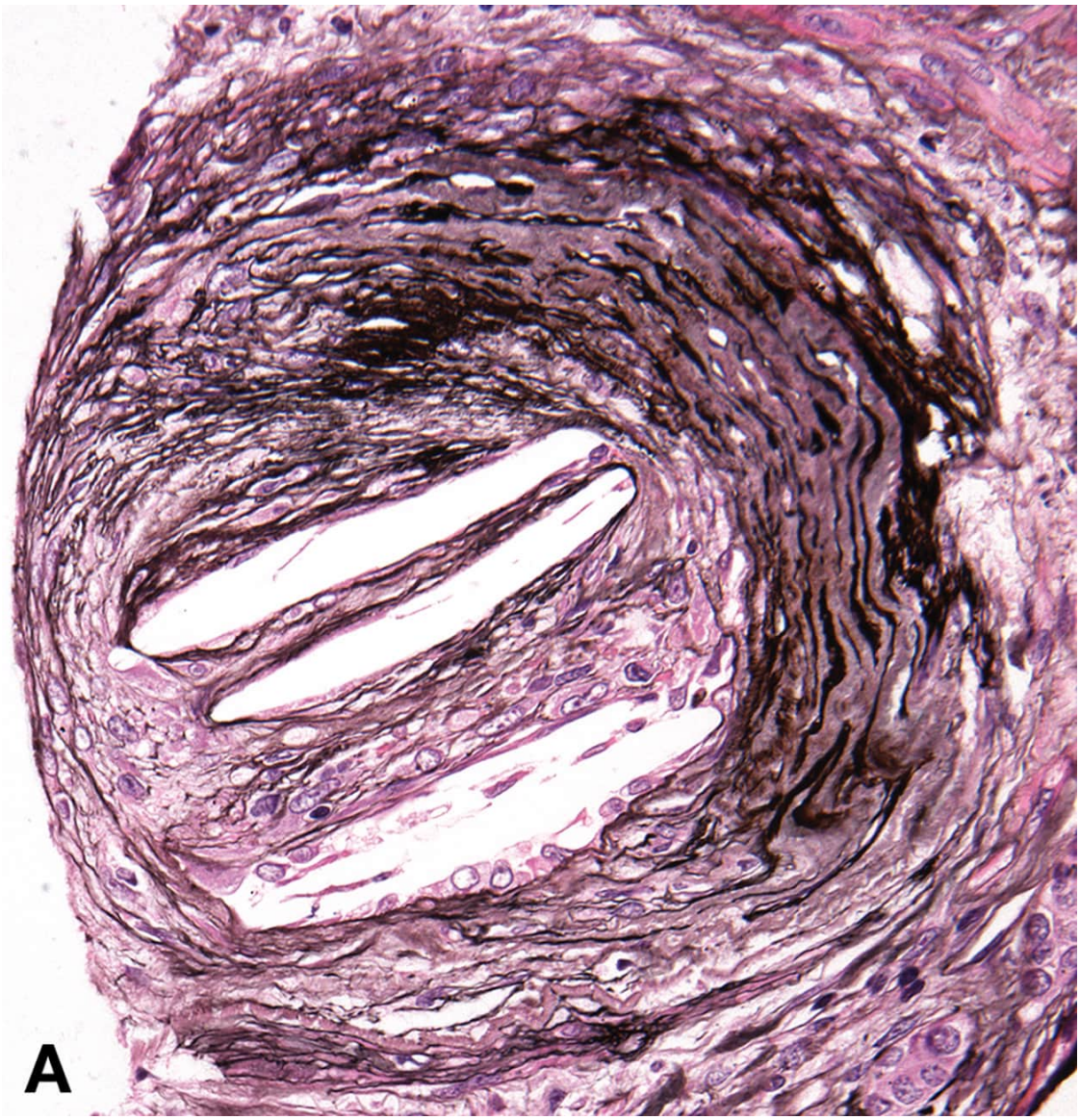
- May occur spontaneously or following invasive arterial procedure, arteriography, vascular surgery, or thrombolytic therapy
- Known as a mimicker as the clinical findings may suggest other diseases (interstitial nephritis, GN, autoimmune disease)

Clinical manifestations

- Patients may present with the classic triad including AKI, livedo reticularis, and eosinophilia.
- Other signs and symptoms may include unexplained fevers, weight loss, myalgias, anorexia, end-organ infarction/injury (eg, stroke, myocardial/bowel/renal infarction, pancreatitis, adrenal failure, muscle infarction).
- Atheroembolic disease may occur weeks to months following the inciting event and involve one or both kidneys.

Diagnostic testing

- Fundoscopic exam may reveal cholesterol emboli aka Hollenhorst plaque.
- Laboratory findings: leukocytosis, eosinophilia, anemia, thrombocytopenia, elevated blood urea nitrogen (BUN) and SCr, hematuria, transaminitis, elevated CPK, amylase, and inflammatory markers (eg, hypocomplementemia, elevated rheumatoid factor, antinuclear antibody, C-reactive protein, and/or sedimentation rate)
- Histopathology: As cholesterol dissolves during tissue processing, embolized cholesterol crystals appear as clear needle-shaped clefts within vascular lumens or walls, with or without fibrin, surrounding multinucleated giant cells or intimal fibrosis depending on the timing of the embolization. Cholesterol clefts may be seen in large or small arteries, arterioles, or capillaries (**Figure 11.4**).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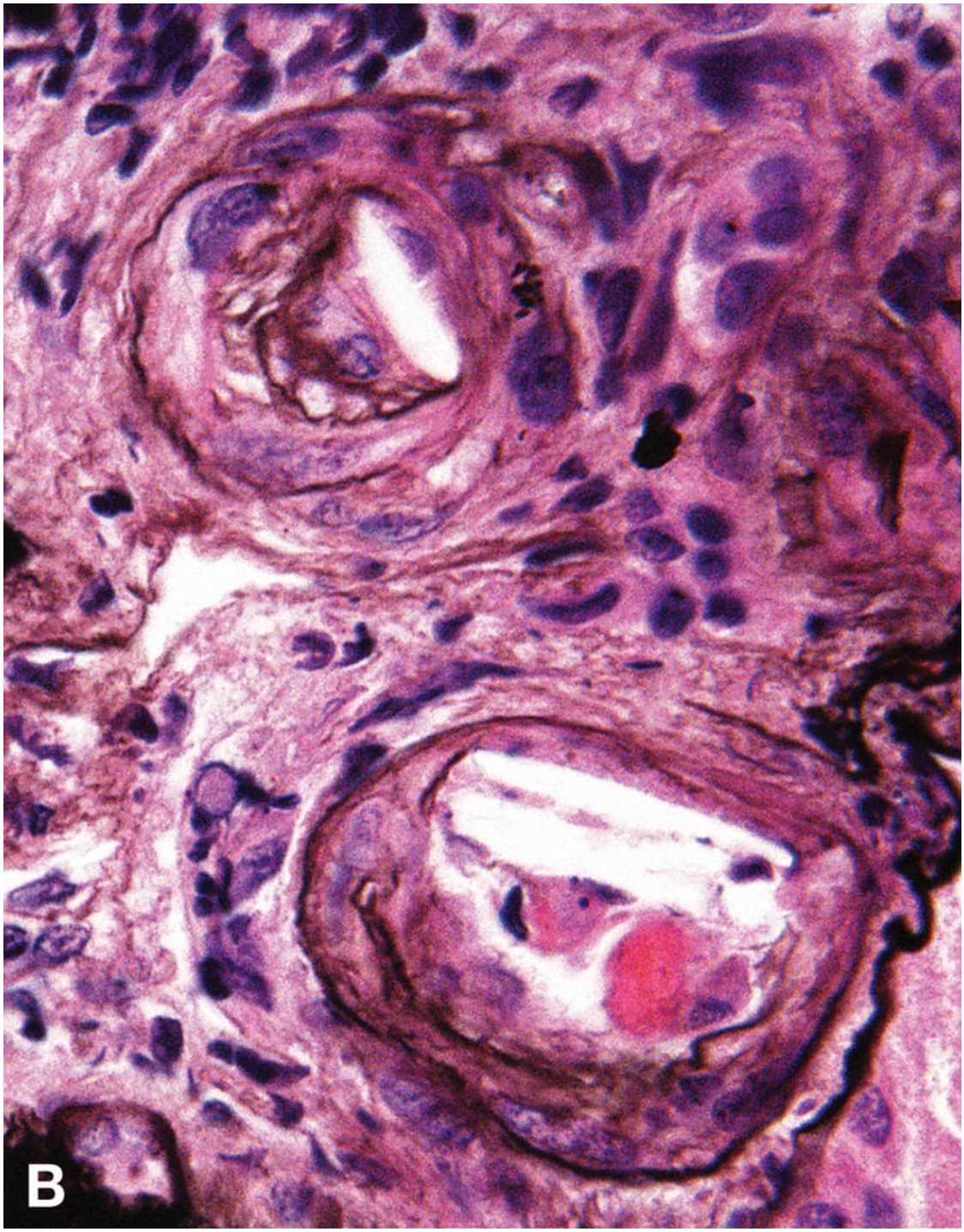


FIGURE 11.4 **Atheroembolus.** A. Artery with clear acicular crystals (cholesterol) embedded in a fibrotic intima, indicative of an older lesion (Jones silver x 600) B. Arterioles with needle-shaped cholesterol crystals in the lumens, associated with endothelial cell swelling and fibrin, indicating recent atheroembolization. (Jones silver x 600).

Management

- Supportive, nutritional support given a high catabolic state in patients with atheroembolic disease
- Avoid further invasive procedures if possible.

- No anticoagulant or thrombolytic should be given due to concerns for possible dislodgment of more atheromatous plaques.

Renal vasculitis

Renal vasculitis is discussed in **Chapter 7: Glomerular and Vascular Disorders**.

Aortic dissection

Aortic dissection or aneurysm may extend into renal arteries and compromise arterial blood flow.

Renal vein thrombosis (RVT)

Risks

- Severe nephrotic syndrome, most commonly membranous nephropathy, followed by minimal change disease and membranoproliferative GN
- External compression: retroperitoneal fibrosis, lymphadenopathy, tumors, adjacent aneurysm
- Hypercoagulable states
- Others: malignant renal tumors extending into renal vasculature, trauma, hyperacute renal rejection, infections, renal collagen vascular diseases, sickle cell nephropathy, pregnancy, estrogen therapy, amyloidosis, diabetic nephropathy, antiphospholipid syndrome, Behçet syndrome

Clinical manifestations: gross or microscopic hematuria, flank pain, AKI; left-sided RVT may lead to gonadal vein thrombosis and cause pelvic congestion in females and left testicular swelling or varicocele in males. Patients may be asymptomatic in chronic RVT.

Diagnosis: Computed tomography (CT) angiography or contrast-enhanced magnetic resonance venography has reported sensitivity and specificity of nearly 100%. Ultrasound with Doppler may be typically done as initial imaging study but may not be sensitive enough to detect small RVT.

Treatment:

- Anticoagulation (eg, low-molecular-weight heparin bridging with warfarin to achieve an international normalized ratio [INR] of 2-3) for 6 to 12 months or until underlying etiology has resolved (ie, nephrotic syndrome has resolved)
- Surgical thrombectomy may be considered in rare cases with acute bilateral RVT and AKI when percutaneous thrombectomy/thrombolysis is not possible.

Glomerular Diseases Causing AKI

- Glomerular diseases associated with nephritic syndrome may present with a rapidly progressive course and AKI.
- Glomerular diseases associated with nephrotic syndrome can cause AKI due to RVT or nephroedema with reduced renal perfusion.
- AKI associated with GN may be due to renal hypoperfusion caused by overdiuresis, nephrotoxic effects from immunosuppressive therapy, acute interstitial nephritis associated with prophylactic antibiotics or proton pump inhibitor (PPI), or anticoagulant-related nephropathy (ARN) with anticoagulation.

See **Chapter 7: Glomerular and Vascular Disorders** for discussions on glomerular and vascular diseases.

Acute Tubulointerstitial Injury

In addition to the following conditions, see **Chapter 6: Tubular, Interstitial, and Cystic Disorders** for other conditions that may present as AKI.

Heme-pigment-induced AKI (hemoglobin [Hb], myoglobin)

Pathogenesis of AKI associated with heme-pigment-induced AKI

- Heme cast formation with uromodulin (Tamm-Horsfall protein) can lead to tubular obstruction.
- Release of free iron induces cellular damage and direct proximal tubular cell injury.
- Circulating heme and free Hb deplete nitric oxide, which can lead to vasoconstriction and renal hypoperfusion. This explains why FeNa may be less than 1% in patients with hemoglobinuria.
- Heme-pigment-induced AKI risks: volume depletion, low urine pH

Hemolysis

- Causes: ABO-incompatible blood transfusions, glucose-6-phosphate dehydrogenase (G6PD) deficiency, poisoning, snake/insect envenomation, drugs (methyldopa, cephalosporins, dapsone, paroxysmal nocturnal hemoglobinuria, malaria)
- Clinical manifestations: fatigue, shortness of breath, dyspnea of exertion, chest pain, AKI
- Laboratory findings: reduced haptoglobin, increased lactate dehydrogenase (LDH) and bilirubin, increased reticulocytes and spherocytes, hyperkalemia

Rhabdomyolysis

- Causes: trauma (crush injury, electric shock), immobilization (particularly patients with morbid obesity), prolonged vascular/orthopedic surgery, extreme exertion (exacerbated by heat, underlying metabolic/inflammatory myopathies), seizures, neuroleptic malignant syndrome, alcoholism (particularly if concurrent electrolyte abnormalities, eg, hypophosphatemia, hypokalemia, hypomagnesemia), drugs/toxins, infections (HIV, influenza, *Legionella*), myositis associated with rheumatologic disorders, ischemic muscle injury, familial disorders
- Clinical manifestations: myalgias, AKI
- Laboratory findings:
  - Elevated CPK
    - CPK levels of greater than 40,000 U/L may be associated with severe AKI.
    - AKI is uncommon with CPK levels of less than 5,000 U/L.
  - Transaminitis (elevated intramyocyte aspartate aminotransferase [AST], alanine aminotransferase [ALT], LDH, and aldolase) may be seen with rhabdomyolysis but not hemolysis.
  - Electrolyte abnormalities: hyperkalemia (Potassium may increase at >1 mEq/L/d vs ~0.3 mEq/L/d in other non-hypercatabolic AKI.), hyperphosphatemia (release from injured muscle cells), hypocalcemia (due to calcium phosphate deposition into injured muscles, reduced bone sensitivity to parathyroid hormone [PTH]), hyperuricemia, metabolic acidosis
- Histopathology: eosinophilic coarse clumped "ropelike" casts with tubular cell injury. Immunohistochemistry staining for myoglobin and Hb allows differentiation of these etiologies.

Urinalysis

Reddish-brown urine can be seen with hematuria, myoglobinuria, hemoglobinuria, or agents with reddish-brown coloring effects (beet, phenazopyridine, porphyria). The following can differentiate the different causes of reddish-brown urine:

- Centrifuge urine:
  - Red sediment suggests hematuria (ie, presence of RBCs in sediment).
  - Red supernatant suggests myoglobinuria, hemoglobinuria, *or* agents with coloring effect.
- Heme dipstick (ie, presence of "blood" on urine dipstick):

- Positive "blood" indicates the presence of either myoglobinuria or hemoglobinuria.
- Negative "blood" is more consistent with agents with coloring effect.

Plasma color may differentiate myoglobinuria from hemoglobinuria

- Clear plasma favors myoglobinuria: Due to its low-molecular weight, myoglobin is easily filtered and does not remain/accumulate in plasma.
- Red/pink plasma favors hemoglobinuria: Hb has a high-molecular weight, binds to haptoglobin, is not easily filtered, and remains in plasma as red/pink color. Hemoglobinuria associated with hemolysis suggests high plasma Hb concentration.

Management of rhabdomyolysis

- Early and aggressive volume administration: Start normal saline (NS) at 100 to 200 mL/h if the patient can produce urine. Aim for goal UO of 200 to 300 mL/h. Monitor volume status.
- Theoretical benefits of normal $NaHCO_3$ over NaCl solutions:
  - If urine pH is raised to greater than 6.5, renal toxicity from heme may be reduced.
  - Reduces pigment cast formation of heme-protein with uromodulin
  - Reduces release of free iron from myoglobin or Hb
  - Despite theoretical benefits above, there is no clear clinical evidence of the benefits of $NaHCO_3$ over NaCl except possibly in severe rhabdomyolysis.
  - MUST avoid $NaHCO_3$ in patients with the following: hypocalcemia, pH greater than 7.4, CO_2 retention, or high Ca-PO_4 products
- Benefits of mannitol remain undefined and not routinely recommended.
- Loop diuretics do not change outcome in AKI. Use in patients with volume overload only.
- The benefit of dialysis to remove myoglobin, Hb, or uric acid has not been shown.

Hyperbilirubinemia

- Severe hyperbilirubinemia, for example, serum bilirubin levels of greater than 20 mg/dL have been reported to be associated with ATN, with bile reabsorption droplets in tubular epithelial cells and bile casts in tubular lumens.
- Kidneys appear green on autopsies.

Hypercalcemia

- May be associated with AKI
- Mechanisms attributable to AKI include volume depletion (nephrogenic diabetes insipidus), calcium phosphate/oxalate precipitation and microtubular obstruction, tubulointerstitial nephritis, and intrarenal vasoconstriction and reduced renal perfusion.

(Radio)contrast-associated AKI (CA-AKI)

- Because of the weaker link between radiocontrast use and AKI, the term contrast-induced AKI has been changed to contrast-associated AKI.
- A 2018 meta-analysis involving 28 studies and 107,335 participants revealed that compared with noncontrast CT, contrast-enhanced CT was not significantly associated with AKI (odds ratio [OR] 0.94; 95% confidence interval [CI] 0.83-1.07), need for KRT (OR 0.83; 95% CI 0.59-1.16), or all-cause mortality (OR 1.0; 95% CI 0.73-1.36).
- The lower incidence of CA-AKI than previously reported may be attributed to the use of newer less nephrotoxic contrast agents and more aggressive preventive strategies in high-risk patients.

Pathogenic mechanisms of CA-AKI

- Medullary hypoxia (radiocontrast induces vasoconstriction of both afferent and efferent arterioles, but greater effect in afferent arterioles)
- Direct cytotoxicity
- Generation of reactive oxygen species

Risks of CA-AKI

- Mehran risk score may be calculated based on the following risk factors: hypotension, intra-aortic balloon pump, congestive heart failure, age above 75 years, anemia, diabetes mellitus, contrast media volume of more than 100 mL, reduced GFR
- Well-controlled diabetes mellitus with normal kidney function likely does not have increased the risk of CA-AKI.

Histopathology: proximal tubular cell cytoplasmic isometric vacuoles

Management/preventive measures

KDIGO 2024 suggests management in accordance with consensus statements from the radiology societies in individuals with AKI or GFR of less than 60 mL/min/1.73 m^2 (CKD G3a-G5) undergoing elective investigation:

- Use low-osmolal or iso-osmolality or iso-osmolarity contrast media.
- Use minimum but adequately effective contrast dose for diagnostic study.
- Withdraw "nonessential potentially nephrotoxic medications, for example, NSAIDs, diuretics, aminoglycosides, amphotericin, platins, zoledronate, and methotrexate in people with AKI or estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 for 24 to 48 hours before and 48 hours after radiocontrast exposure."
- For metformin users:
  - In individuals with eGFR of greater than 30 mL/min/1.73 m^2 and without evidence of AKI: Metformin does not need to be stopped before iodinated contrast study. There is no need to reevaluate GFR after the study.
  - In individuals with eGFR of less than 30 mL/min/1.73 m^2: "It is appropriate to hold metformin at the time of or before iodinated contrast media injection." Metformin "should not be restarted for at least 48 hours and only then if GFR remains stable and the ongoing use of metformin has been reassessed by the clinical team."
- For renin-angiotensin-aldosterone system inhibitors (RAASi) users:
  - Consider withholding RAASi in at-risk individuals for 48 hours or more before elective contrast CT to avoid the potential risk for hypotension and hyperkalemia if CA-AKI develops.
  - RAASi may be restarted if CA-AKI does not occur or after the return of GFR to baseline.
- Avoid dehydration.
  - Compared with NS, intravenous sodium bicarbonate provides no added benefits. The 2018 PRESERVE (Prevention of Acute Kidney Injury After Contrast Administration) trial (Outcomes after angiography with sodium bicarbonate and *N*-acetylcysteine [NAC]) revealed no benefit of intravenous sodium bicarbonate over sodium chloride or of oral NAC over placebo for the prevention of death, need for KRT, persistent increase of 50% or more from baseline SCr at 90 days, or the prevention of CA-AKI.
  - American College of Radiology guidelines suggested hydration protocol for the inpatient setting: 100 mL/h (isotonic solution) beginning 6 to 12 hours before and continuing 4 to 12 hours after (for nonoliguric patients or those with anuria). Must monitor volume status closely.

  - Fluid tonicity: Isotonic is preferred over one-half isotonic saline.
  - For patients with congestive heart failure, focus on maintaining euvolemia. That is, the use of diuretics (not intravenous hydration) may be necessary in volume-overloaded patients to achieve optimal cardiac contractility and cardiac output, thus renal perfusion.
  - Outpatient oral hydration: Salt-containing fluids, for example, soups, are likely better than water.
- "Use of NAC, ascorbic acid, furosemide, dopamine, fenoldopam, or calcium channel blockers as preventive measures of CA-AKI has not been shown to be a consistent benefit."
- "Prophylactic pericontrast hemodialysis has been shown to be potentially harmful and is not recommended." Expert opinion regarding hemofiltration or hemodialysis for CA-AKI prevention:
  - For patients on established dialysis, immediate dialysis is not needed unless other indications exist, for example, volume overload or hyperkalemia.
  - In patients with pre-ESKD, dialysis initiation for the sole indication of CA-AKI is not recommended.

Drug-induced AKI

See **Chapter 10: Pharmacology**.

Viral-associated AKI

Hantavirus infection (most commonly subtype Puumala) is associated with flu-like symptoms and acute kidney failure: Reported biopsy findings include tubulointerstitial nephritis, medullary hemorrhage, interstitial edema, and tubular cell necrosis. Podocyte effacement in association with glomerular proteinuria has been described.

H1N1 influenza A: AKI is common and predominantly associated with ATN with or without rhabdomyolysis. The latter is typically mild and does not cause AKI. AKI requiring kidney replacement therapy has been reported to be approximately 20%.

COVID-19

- Causes of AKI: ATN, rhabdomyolysis, TMA, GN (collapsing focal segmental glomerulosclerosis [FSGS] in patients with high-risk APOL1 alleles, IgAN, and others)
- Risks for AKI: older age, diabetes mellitus, HTN, heart failure, higher body mass index, underlying CKD, severe hypoxemia
- The presence of AKI was associated with increased mortality. Nonetheless, Aklilu et al reported that in a retrospective multicenter cohort study, hospitalized survivors of COVID-AKI had lower rates of major adverse kidney events, long-term kidney function decline, and mortality compared with patients with AKI associated with other illnesses.
- Patients who required mechanical ventilation were more likely to require KRT.
- Approximately one-third of patients who required KRT for AKI needed maintenance KRT at the time of discharge.
- Management: volume replacement as needed, correction of electrolytes, replete electrolytes as needed in those affected with severe diarrhea

AKI in Patients With Cancer

Tumor lysis syndrome (TLS)

TLS may occur spontaneously with high cellular proliferation and rapid cellular turnover or following chemotherapy for a large tumor burden. Lysis of tumor cells releases large amounts of potassium, uric acid, and phosphates that can cause multiorgan injury. Hypocalcemia can occur due to sequestration into injured tissues or systemic coprecipitation with phosphates.

Risks

- Malignancies at high risk for TLS
  - Advanced Burkitt lymphoma/leukemia or early disease with elevated baseline LDH
  - Acute lymphocytic leukemia (ALL) (WBC >10,000/mL or LDH ≥2 times upper limit of normal [ULN])
  - Acute myeloid leukemia (AML) (WBC >10,000/mL)
  - Diffuse large B-cell lymphoma with baseline LDH 2 times or more the ULN
- Elevated LDH level (ie, ≥2 times ULN) before treatment (LDH is released with cell death. High LDH level indicates high degree of cell lysis/cell death.)
- Reduced kidney function before treatment

The diagnosis of TLS is based on laboratory and clinical findings (**Table 11.3**)

Table 11.3 Diagnosis of tumor lysis syndrome: laboratory versus clinical criteria

Laboratory criteria Having two or more of the following	Clinical criteria
Hyperuricemia: serum uric acid ≥8 mg/dL or ≥25% increase from baseline	Meeting laboratory criteria
Hyperkalemia: serum potassium ≥6 mEq/L or ≥25% increase from baseline	PLUS
Hypocalcemia: serum total calcium <7 mg/dL or ≥25% decrease from baseline	Having one or more associated complications involving acute kidney injury, cardiac arrhythmia due to severe hyperkalemia, and/or hypocalcemia, seizures, or death
Hyperphosphatemia: serum phosphate >6.5 mg/dL or ≥25% increase from baseline	

- Criteria for laboratory TLS: two or more of the following:
  - Hyperuricemia: uric acid levels of 8 mg/dL or higher, or 25% or greater increase from baseline
  - Hyperkalemia: potassium levels of 6 mEq/L or higher, or 25% or greater increase from baseline
  - Hyperphosphatemia: phosphorus levels of greater than 6.5 mg/dL, or 25% or greater increase from baseline
  - Hypocalcemia: calcium levels less than 7 mg/dL, or a decrease of 25% or greater from baseline
- Criteria for clinical TLS:
  - Meeting laboratory criteria above PLUS
  - One or more of associated complications including AKI, cardiac arrhythmias (due to severe hyperkalemia and/or hypocalcemia), seizures, or death

Etiologies of AKI associated with TLS

- Hyperuricemia:
  - Tubular obstruction from uric acid crystallization
  - Uric acid–induced inflammatory response, ATIN
  - Uric acid–induced renal vasoconstriction

- Hyperphosphatemia: tubular obstruction from calcium oxalate crystals

Treatment of TLS

- Prevention is key:
  - Volume expansion with crystalloid solutions to maintain UO 80 to 100 mL/h
  - Urinary alkalinization to increase uric acid solubility is no longer routinely recommended due to poor efficacy while exposing patients to potential complications of alkalinization (eg, reduced ionized calcium level, increased risk of calcium phosphate precipitation, CO_2 retention, and narcosis in CO_2 retainers).
  - Dietary potassium and phosphorus restriction
- Management of hyperuricemia:

Purine metabolites of nucleic acids are converted to uric acid via a multistep process requiring the enzyme xanthine oxidase (XO) (**Figure 11.5**). Uric acid level may be reduced by blocking its production or increasing its metabolism to a soluble and excretable metabolite called allantoin.

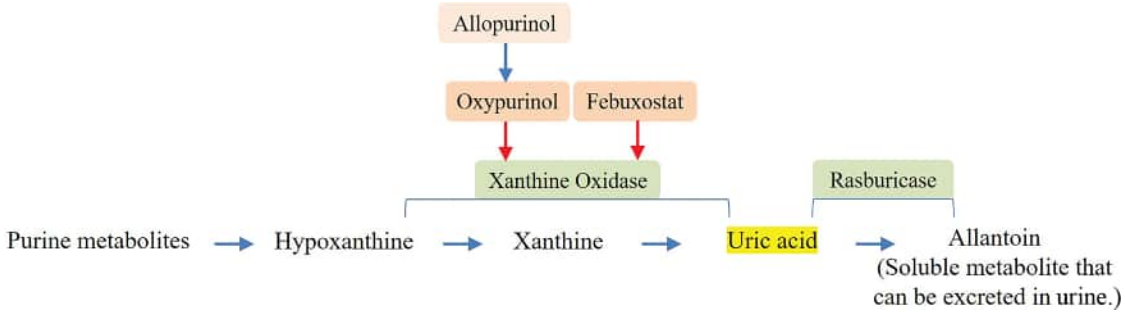


FIGURE 11.5 Metabolism of purine metabolites. Purine metabolites of nucleic acids are metabolized to uric acid via a multistep reaction requiring the enzyme xanthine oxidase. Allopurinol is converted to oxypurinol, a competitive inhibitor of xanthine oxidase, to decrease downstream uric acid formation. Febuxostat is a non-purine xanthine oxidase inhibitor that also acts to reduce downstream uric acid formation. Both allopurinol and febuxostat cannot reduce preexisting uric acid levels. Rasburicase is a recombinant form of urate oxidase that can convert uric acid into the more soluble metabolite allantoin, which can be renally excreted. Rasburicase can, therefore, effectively remove uric acid from the body. Blue arrows indicate steps in metabolism. Red arrows indicate inhibition. Xanthine oxidase metabolizes hypoxanthine and xanthine to uric acid. Rasburicase metabolizes uric acid to allantoin, a soluble metabolite that can be excreted into the urine.

- Agents that block uric acid production:
  - Allopurinol is converted to oxypurinol, a competitive inhibitor of XO to decrease uric acid formation. Allopurinol can reduce uric acid production but cannot reduce *preexisting* hyperuricemia.
  - Febuxostat is a non-purine XO inhibitor that is commonly used for the treatment of hyperuricemia associated with gout. A 2019 meta-analysis involving 658 patients revealed similar efficacy to allopurinol in terms of lowering uric acid levels and tumor lysis incidence. Of note, febuxostat has the warning label "Gout patients with established cardiovascular (CV) disease treated with febuxostat tablets had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study."
- Agent to metabolize uric acid to a soluble and excretable form:
  - Rasburicase is a recombinant urate oxidase that converts uric acid to the more soluble metabolite, allantoin, which can be renally excreted.
  - Rasburicase effectively reduces hyperuricemia but has not been shown to reduce the incidence of clinical TLS.
  - Caution: Rasburicase is associated with hypersensitivity (including anaphylaxis) in 1% of patients and is contraindicated in patients with G6PD and catalase deficiencies due to the

development of hemolytic anemia and methemoglobinemia.

- KRT as needed for patients with TLS-associated severe AKI

Hematopoietic stem cell transplant (HSCT)-associated AKI

HSCT requires three steps including conditioning before HSCT (myeloablative, reduced intensity, or nonmyeloablative therapy), actual HSCT procedure, and engraftment. HSCT-associated AKI generally reflects procedures and immunosuppressive regimens used and patient response at each phase.

Conditioning (myeloablative, reduced intensity, or nonmyeloablative therapy)

- In cases where immunosuppressive therapy is used, for example, CNI, CNI-associated AKI, or TMA may occur.
- There is a higher risk of AKI associated with myeloablative compared with nonmyeloablative therapy, likely due to the higher intensity of immunosuppression and associated complications.

Actual HSCT

- Use of immunosuppressive therapy, for example, CNI, may result in CNI-associated AKI or TMA.
- Perioperative complications and associated treatment, for example, use of antibiotics and/or PPIs, postoperative urinary retention, can increase AKI risks.

Engraftment

- Engraftment syndrome with its proinflammatory state causing endothelial cell injury and cytokine release and associated capillary leak and intravascular volume depletion can lead to renal hypoperfusion and ATN. Patients with engraftment syndrome may manifest with fevers, rash, and noncardiogenic pulmonary edema.
- Hepatic sinusoidal obstruction syndrome due to damage of sinusoidal endothelial cells and narrowing of small hepatic venules results in portal HTN, manifests as fluid retention, jaundice, and painful hepatomegaly. This is followed by reduced renal perfusion and ATN.

Infectious complications

- Bacterial and viral infections (eg, cytomegalovirus [CMV], human herpesvirus 6, and BK virus) may also be associated with TMA.
- Antimicrobial-associated AKI may also be considered.

Long-term complications

- Nephrotic syndrome, for example, membranous nephropathy (the most common), and minimal change disease may manifest. These GNs are thought to be related to graft-versus-host disease.
- CKD has been reported in up to 50% of patients.

Management

- Preventive:
  - Minimize nephrotoxic conditioning regimens.
  - Use immunosuppressive therapy other than CNI if possible, particularly in patients with CKD.
  - Use of letermovir prophylaxis for CMV to reduce the need for nephrotoxic foscarnet.
- Supportive care and treatment of any reversible cause.

Chemotherapy/antineoplastic agents

See **Chapter 10: Pharmacology** for discussions on the effects of commonly used chemotherapy agents on the kidneys.

AKI in Pregnancy (Table 11.4)

Table 11.4 Pregnancy-related causes of acute kidney injury over the course of pregnancy

Time of onset	First trimester	Second to third trimester[a]			Third trimester	Postpartum
Conditions	Hyperemesis gravidarum	PE/E Onset >20 wk	HELLP	TTP	Acute fatty liver of pregnancy	Complement-mediated HUS
Presentation: signs and symptoms	**Intractable N/V** with inadequate fluid intake	Epigastric/RUQ pain, N/V, HA, blurry vision, sudden onset edema	Chest pain, RUQ pain, N/V, HA; may occur postpartum and in 20% with PE/E	±Fevers, HA ±Altered mental status; ±neurologic symptoms	Malaise, N/V Abdominal pain ±Edema (associated with kidney failure)	May occur up to 6 mo **postpartum**; may be triggered by infections, bleeding
Physical examination: characteristic findings	±↓BP, ±↑pulse Dry oral mucosa	↑↑**BP,** +peripheral and pulmonary **edema** ±Neurologic deficits, ±seizures	±↑BP ±Ecchymosis ±Jaundice	±↑BP, ±fever ±Disorientation, ataxia, ±neurologic deficits, ±seizures	±↑BP Hepatic encephalopathy **Jaundice;** **ascites**	↑BP ±Edema (associated with kidney failure)
Complete blood count and smear	±↑Hb No schistocyte	±↓Hb, ±↓platelets ±Schistocytes	↓Hb, +schistocytes, ↓↓**platelets**	↓Hb, ±schistocytes, ↓↓**platelets**	↑WBC, ±↓platelets ±↓Hb; ~no schistocyte	↓Hb, ±schistocytes ↓↓**Platelets**
Metabolic panel	↑BUN/SCr	±↑SCr; ↑uric acid	±↑SCr	±↑SCr	Hypoglycemia; ±↑SCr	↑↑SCr
LDH	Normal LDH	±↑LDH	**LDH >600 U/L**	↑**LDH**	±↑LDH	↑**LDH**
Coagulation studies	Normal	±↑PTT, ±↓fibrinogen, ±↑FDP	±↑PTT, ±↑FDP, and ±↓fibrinogen	**Normal PTT, fibrinogen, and FDP**	↑**PT,** ↓**fibrinogen,** ↓**antithrombin III**	**Normal PTT, fibrinogen, and FDP**
Liver function	Normal	±Transaminitis	**++Transaminitis**	±Transaminitis	**++Transaminitis**	±Transaminitis
Urinalysis	↑SG, **hyaline or muddy brown casts**	±Proteinuria	±Proteinuria	+Blood ++Proteinuria	±Proteinuria ±Pigmented casts **++Bilirubin**	+Blood ++Proteinuria
ADAMTS13	Normal activity	Normal-low activity	Normal-low activity	↓**Activity to <10%**	Normal activity	Normal-low activity
Management	Supportive	Delivery	Delivery	Plasma exchange	Delivery	Ecu- or ravu-lizumab
Renal prognosis	Good	Good	Good	Good	Good	High risk for ESKD

Abbreviations: ADAMTS13, A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; BP, blood pressure; BUN, blood urea nitrogen; ESKD, end-stage kidney disease; FDP, fibrinogen degradation product; HA, headache; HELLP, **H**emolysis **E**levated **L**iver enzyme and **L**ow **P**latelet; LDH, lactate dehydrogenase; N/V, nausea, vomiting; PE/E, preeclampsia/eclampsia; PT, prothrombin time; PTT, partial thromboplastin time; RUQ, right upper quadrant; SCr, serum creatinine; SG, specific gravity; TTP, thrombotic thrombocytopenic purpura; WBC, white blood cell.

[a]Obstructive uropathy with associated acute kidney injury (AKI) may also be seen in late second to third trimester of pregnancy. A kidney ultrasound should be part of the routine evaluation for AKI in pregnancy. Bolded texts highlight unique characteristics of the different conditions.

- Early: before 20 weeks gestational age: volume depletion due to hyperemesis gravidarum with poor oral intake, septic abortion
- After 20 weeks to postpartum: bleeding (eg, placenta abruption), preeclampsia/eclampsia, HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets), TTP, acute fatty liver of pregnancy (AFLP), pregnancy-associated complement-mediated HUS (previously known as atypical HUS), bilateral renal cortical necrosis, obstructive uropathy, recurrence/relapse of underlying glomerular diseases. Preeclampsia/eclampsia and HELLP are discussed in **Chapter 5: Hypertension**.

Thrombotic thrombocytopenic purpura

- Pathogenesis: During normal pregnancy, ADAMTS-13 level (A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) tends to be decreased during the last trimester while von Willebrand factor level is increased. These physiologic changes are thought to prepare the mother for optimal clotting at delivery to minimize blood loss. Individuals with low but clinically adequate ADAMTS-13 levels in the nonpregnant state may be at risk for TTP during the second and third trimesters of pregnancy when ADAMTS-13 levels are further depressed.
- Clinical manifestations: fevers, headaches, altered mental status, neurologic symptoms, seizures, AKI
- Laboratory findings: TMA, thrombocytopenia, elevated LDH, normal partial prothrombin time and fibrinogen, ADAMTS-13 activity less than 10%
- Management: Plasma exchange

Acute fatty liver of pregnancy

- Pathogenesis: Fetal deficiency of long-chain 3-hydroxyl coenzyme A dehydrogenase leads to excess fetal free fatty acids that cross the placenta and induce maternal hepatotoxicity.
- Clinical manifestations: anorexia, nausea, vomiting, ascites, AKI
- Laboratory findings: marked transaminitis, coagulopathy, hypoglycemia. There is no hemolytic anemia.
- Management: delivery, supportive care, correction of coagulopathy with infusions of fresh frozen plasma (FFP), blood, or cryoprecipitate as needed, monitor and treat hypoglycemia.

Complement-mediated HUS of pregnancy

- Pathogenesis: thought to be due to the loss of placental regulatory proteins that normally protect against alternative complement pathway activation (ACP). Susceptible individuals are those who have mutations of complement regulatory proteins factor H, factor I, C3, and/or membrane cofactor protein. Inciting events for ACP and subsequent HUS of pregnancy have been suggested to include bleeding and infectious complications with delivery.
- Clinical manifestations: Postpartum hemolytic anemia, thrombocytopenia, normal partial prothrombin and fibrinogen, AKI may develop cortical necrosis.
- Management: eculizumab or ravulizumab (humanized monoclonal anti-C5 antibodies)
- Prognosis: 70% to 80% of pregnancy-associated HUS develop ESKD.

Other pregnancy-associated etiologies of AKI

Obstruction

- Late pregnancy: Large uterus compressing on ureters, right-sided involvement is more common, resolves with delivery. Advise positional changes while sleeping.

- Postpartum: Consider injury of soft tissues surrounding urethra or urethra itself with marked inflammation and resultant obstruction of urine flow.

Acute bilateral renal cortical necrosis

- Associated with severe hypotension, typically with severe bleeding
- Clinical manifestations: oliguria or persistent anuria
- Diagnostic imaging: Pericortical rim due to infarction may be seen on CT.
- Histopathology: There is a complete loss of nuclei in affected glomeruli and tubules while the underlying connective tissue framework is preserved.

Other etiologies not related to pregnancy should also be ruled out. Although rare, peripartum cardiomyopathy may be considered if clinically indicated.

KRT in pregnancy

- KRT initiation is generally recommended at eGFR less than 20 mL/min/1.73 m^2 or BUN greater than 50 mg/dL.
- Increasing dialysis dose improves gestational age, live birth rates, and birth weight and reduces rates of maternal HTN and polyhydramnios.
- Earlier dialysis initiation and more intensive dialysis are associated with better maternal and fetal outcomes.

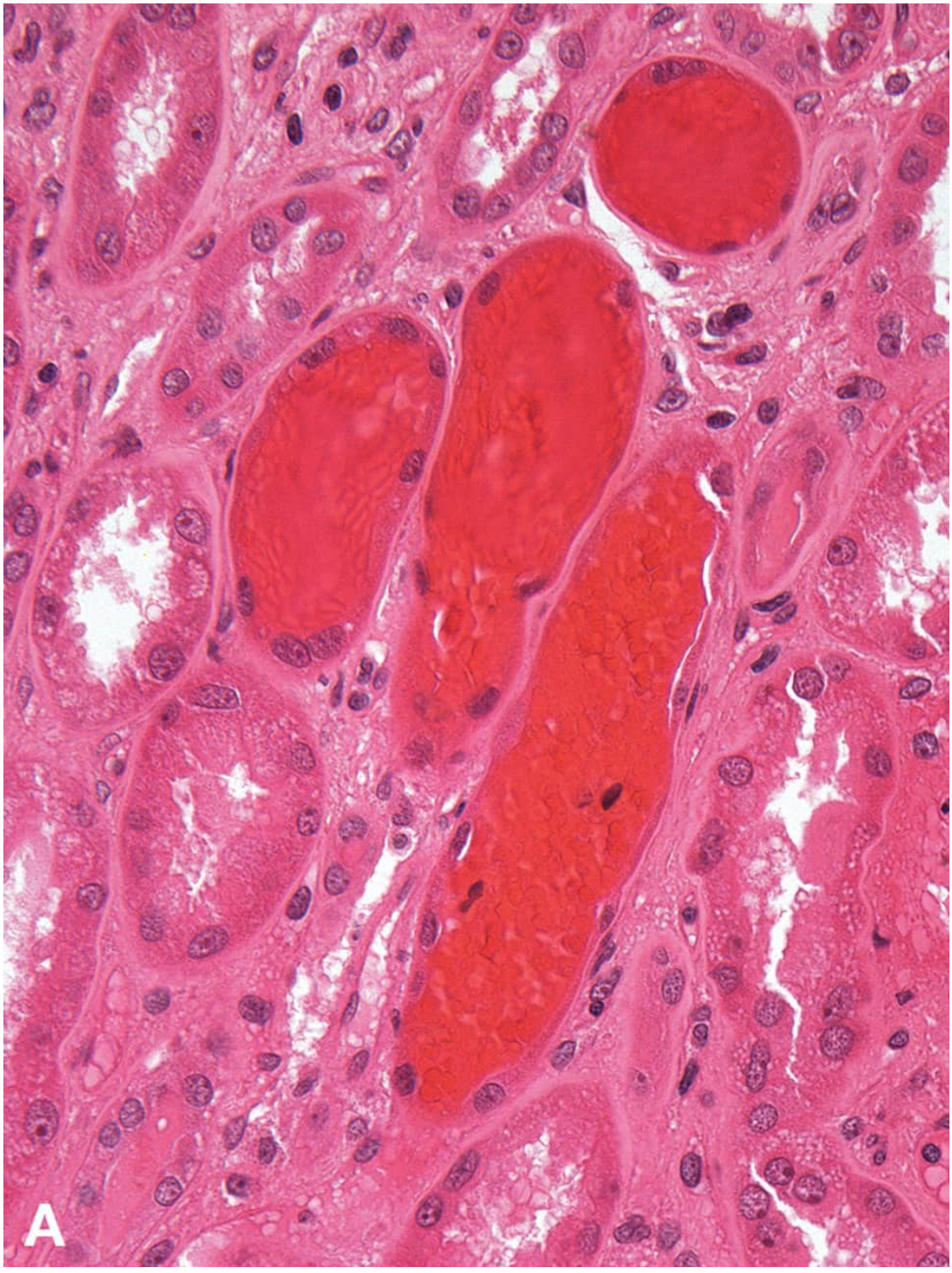
See **Chapter 4: Chronic Kidney Disease** for a more detailed discussion on KRT in pregnancy.

Postrenal (Obstructive) AKI

- Obstructive uropathy refers to structural or functional changes in the urinary tract that adversely affect urine flow. Obstruction may be complete or partial and may involve upper or lower collecting systems and unilateral or bilateral systems.
- Obstructive nephropathy refers to kidney injury due to impaired urine flow.

Intra-collecting system obstruction

- Stones/calculi (kidney or bladder)
- Malignancies: transitional cell carcinoma, monoclonal light chains
- Vascular-related causes: blood clots, sloughed papillae from papillary necrosis (eg, excessive NSAIDs, sickle cell disease, diabetics, renal tuberculosis), ARN
- ARN may be seen in patients receiving antiplatelet or anticoagulation therapy, where intraglomerular bleeding and leakage of RBCs cause tubular obstruction. Risks: older age, diabetes mellitus, HTN, CV disease, over-anticoagulation, for example, INR greater than 3
  - Histopathology: RBCs are predominantly in distal tubular lumens causing obstruction and in glomerular urinary spaces without necrosis or crescent formation (**Figure 11.6**).
- Infections: fungus balls, intra-collecting system abscess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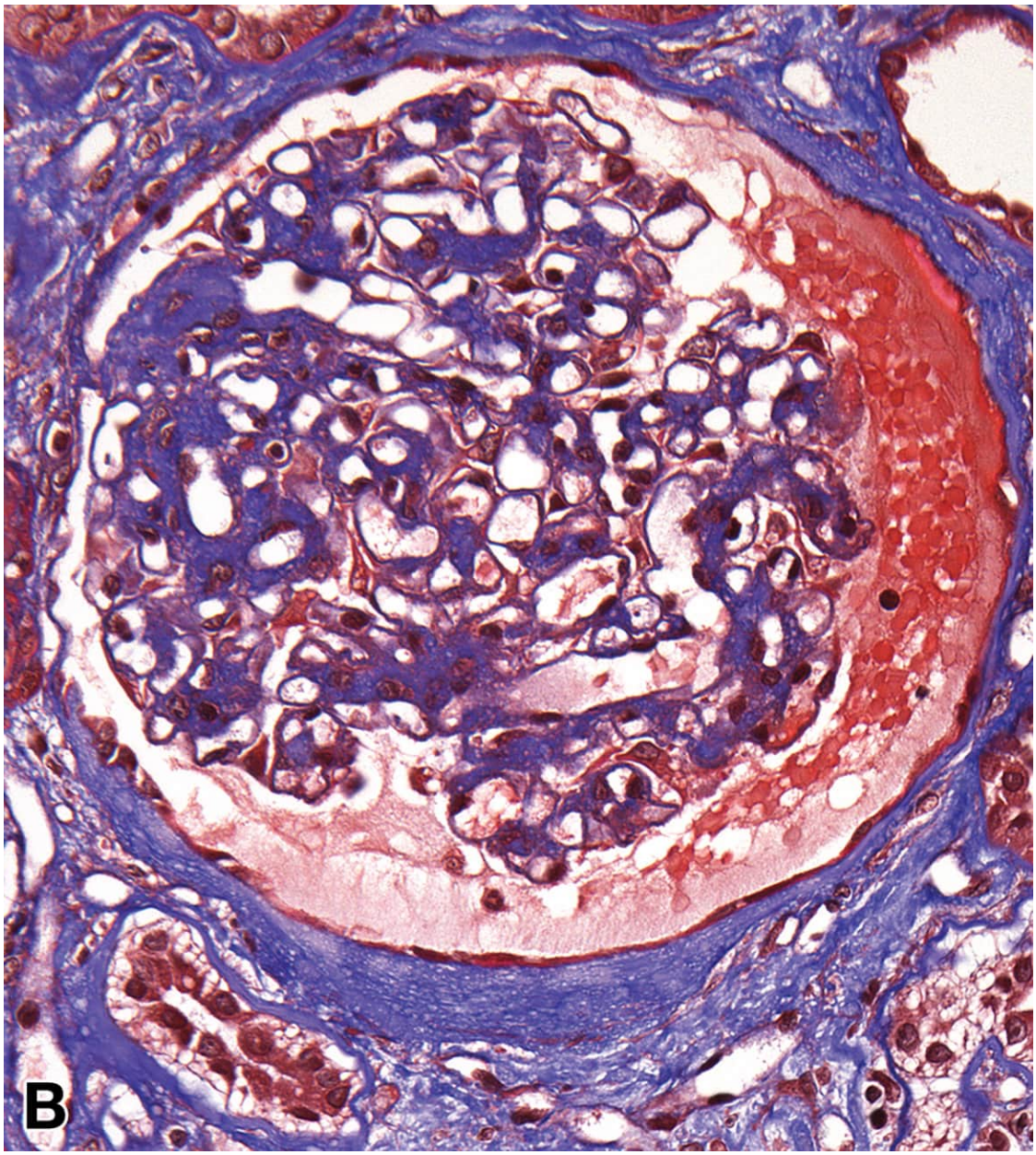


FIGURE 11.6 **Anticoagulant-related nephropathy.** A. Tubules with luminal red blood cells causing luminal dilatation and obstruction. Note the absence of Tamm-Horsfall protein (H&E × 200). B. Glomerulus with red blood cells in the urinary space without necrosis, cells or crescent formation (Trichrome × 400).

Extrinsic compression of collecting system

Common causes to consider: malignancy (particularly female pelvic and gastrointestinal [GI] malignancies), prostate hypertrophy or malignancy, pregnancy (typically right-sided involvement but uncommon cause of AKI). If AKI occurs, renal function recovers within 2 to 3 weeks postpartum.

Retroperitoneal fibrosis (RPF)

- RPF may arise from exaggerated local inflammatory response to aortic atherosclerosis, tissue injury, or autoimmune disease (eg, immunoglobulin G4–related disease [IgG4-RD]).

- Etiologies: idiopathic, drug induced (eg, ergot derivatives, methysergide, bromocriptine, β-blockers, methyldopa, hydralazine, analgesics), infections, malignancies, prior surgeries or retroperitoneal hemorrhage, radiation therapy, smoking, asbestos exposure
- Clinical manifestations: nonspecific back pain, abdominal pain, or lower flank pain that may radiate to inguinal area (testicular pain), testicular hydrocele, nonspecific constitutional symptoms of malaise, weight loss, fevers, nausea/vomiting, constipation, symptoms associated with mesenteric ischemia, upper leg claudication, lower extremity phlebitis or unexplained deep vein thrombosis (DVT), new-onset HTN, elevated erythrocyte sedimentation rate or C-reactive protein levels, obstructive uropathy, tubulointerstitial nephritis if RPF is from IgG4-RD
- Diagnosis: CT scan (may be seen as mass encasing anterior and lateral sides of aorta, often also encasing and compressing IVC, thus tendency for DVT), tissue biopsy (particularly to rule out underlying infections/malignancy)
- Management: relief of obstruction (eg, ureteral stenting, nephrostomy, anti-inflammatory medical therapies such as glucocorticoids)

Collecting system malformations or strictures: phimosis, meatal stenosis, urethral or ureteral strictures from recurrent infections, manipulations

Functional obstruction

- Diabetic neurogenic bladder
- Massive UO that exceeds the patient's ability to void, for example, severe diabetes insipidus
- Drugs that can lead to neurogenic bladder:
  - Anticholinergics (tricyclic antidepressants, diphenhydramine): reduce bladder detrusor muscle contraction
  - NSAIDs: inhibit prostaglandin-mediated detrusor muscle contraction
  - Sympathomimetics: α-Adrenergic agents increase tone in prostate and bladder neck.

Obstruction in the transplant setting

- Ureteral strictures due to trauma, ischemia, or BK virus infection
- External compression by lymphoceles
- Bladder dysfunction (ie, small shrunken bladder from prolonged anuria pretransplant)

Pathogenesis of obstructive kidney injury

- Urinary obstruction leads to increased intratubular pressure which opposes and reduces glomerular filtration. The reduced filtration pressure leads to local renal vasoconstriction, a process mediated by angiotensin II and thromboxanes.
- Subsequently, there is an influx of inflammatory cells and synthesis and release of transforming growth factor-β, inflammatory cytokines, proteases, and oxygen free radicals all acting to induce local tissue injury and fibrosis.
- Histopathology: Tamm-Horsfall protein in proximal tubules and the glomerular urinary space, proximal to its area of production in the distal tubule, with resulting tubular rupture and interstitial Tamm-Horsfall protein, tubular atrophy, interstitial fibrosis, and glomerulosclerosis

Clinical manifestations of obstructive uropathy

- Reduced UO: partial reduction in UO to anuria
- Anuria: Consider lower tract obstruction (bladder neck or urethral obstruction), clotted Foley catheter, bilateral ureteral (papillary necrosis, large tumors).

NOTE

Having a "good" UO does not necessarily imply the absence of obstruction. Patients may still have partial or unilateral obstruction.

- Pain, HTN, sensation of incomplete voiding, suprapubic tenderness or fullness, sometimes with mass-like effect from distended bladder, frequency, nocturia, overflow incontinence, microscopic hematuria, pyuria (may be sterile), stones/crystalluria, tissue from sloughed papillary necrosis

Laboratory findings of obstructive kidney injury

- Elevated SCr unless unilateral obstruction in the setting of normal kidney function in contralateral kidney
- Hyperkalemia and metabolic acidosis out of proportion to the degree of kidney injury
- Elevated BUN to creatinine ratio may be seen due to tubular reabsorption of urea with urinary stasis.

Diagnostic imaging studies for obstructive uropathy

Ultrasound: inexpensive, readily available

False negative for obstruction may be seen in severe volume depletion, oliguric state (eg, concurrent oliguric or anuric ATN), or retroperitoneal fibrosis.

CT urogram or CT-kidney ureter bladder without contrast

- Avoid in child-bearing age women due to radiation exposure.
- Consider CT imaging in unknown causes of hematuria or suspicion for small stones/lesions not detectable or well characterized by ultrasound. CT with contrast is typically obtained for patients aged 50 years and older or those with increased malignancy risk or high clinical suspicion for malignancy.
- Radiocontrast is generally safe for patients with stable eGFR of 45 mL/min/1.73 m^2 or greater assuming all other risks have been minimized.

Magnetic resonance imaging with or without gadolinium

- No radiation exposure
- Poor visibility for stones
- Exercise caution in selection of gadolinium type in patients with CKD. See **Chapter 4: Chronic Kidney Disease**.

Imaging findings

- Cortical thinning implies long-standing obstruction, hence poor function recovery potential.
- Ureteral obstruction with an empty bladder indicates obstruction at the ureteral orifice or more proximal segments.
- Hydronephrosis in patients with a ureteral stent in the presence of a full bladder does not necessarily imply obstruction since the pressure from the full bladder can be transmitted up to the kidneys via the ureteral stent.
- Doppler imaging showing "ureteral jets" signifies urine flow from ureter into bladder.

Management of obstructive kidney injury

Relief of obstruction

- Removal of the source of obstruction or extrinsic compression if applicable and possible
- Foley insertion for bladder neck obstruction; ureteral stenting for ureteral obstruction; nephrostomy placement for obstruction proximal to proximal ureters
- Note that postobstructive diuresis may occur following relief of obstruction. The reasons for postobstructive diuresis include:

- Appropriate diuresis of accumulated sodium/water retention during kidney failure
- Osmotic diuresis from accumulated urea, toxins/solutes during kidney failure
- Obstruction-induced tubular dysfunction and nephrogenic diabetes insipidus (may be transient or chronic)
- Increased atrial natriuretic peptide (ANP) during obstructive period
- Delayed tubular function recovery relative to glomerular filtration recovery. The filtered sodium and water cannot be adequately reabsorbed by the recovering tubules.
- Excessive fluid administration in the postobstructive period

Correction of functional obstruction

- Discontinue responsible medications.
- Consider adding α-adrenergic blockers, such as, tamsulosin, in diabetic neurogenic bladder.
- Treat diabetes insipidus if etiologic.

Management of postobstructive diuresis/polyuria

- Typical fluid replacement: ½ mL of fluid for every milliliter of UO above 100 mL/h with ½ NS. Note that excessive fluid replacement can contribute to polyuria. In patients with continuing polyuria, evaluate for electrolyte diuresis.

([Urine Na + Urine K] × 2/Urine osmolality) > 0.7 may indicate that the polyuria is associated with excessive saline fluid replacement.

- For young patients who can take oral fluid, encourage oral fluid intake.
- Monitor serum potassium and magnesium levels and replete as needed.

Prognosis of obstructive kidney injury

- Prognosis depends on duration, severity, preexisting CKD, and the extent of kidney mass affected (ie, one or two kidneys involved).
- Functional recovery typically occurs by 7 to 10 days following relief of obstruction. Recovery may take longer in more severe and prolonged cases.

Management of AKI

In general, the management of AKI relies on the prevention, prompt removal or correction of contributing factors, optimization of hemodynamics, avoidance of potential nephrotoxins, NSAIDs, and control of hyperglycemia.

Specific AKI prevention considerations in various surgical settings

Off-pump versus on-pump coronary artery bypass grafting (CABG)

- Potential benefits of off-pump: reduced AKI, neurologic complications, strokes, ICU and hospital stays, and mortality
- Potential risks: hemodynamic instability; risks may be minimized with surgeons and anesthesiologists' experience.
- Definitive data supporting the preferential use of on- versus off-CPB pump CABG are lacking.
- KDIGO 2012 suggests that off-pump CABG surgery not be selected solely for the purpose of reducing perioperative AKI or need for KRT.

Sodium bicarbonate infusion during cardiac surgery requiring CPB

- Benefits thought to be via reduced hemoglobinuria-induced nephrotoxicity via urinary alkalinization and/or reduced generation of CPB-induced oxygen free radicals produced by ischemia-reperfusion and inflammation

- In a double-blind randomized control pilot trial involving 100 cardiac surgical patients at risk for postoperative AKI, the incidence of AKI decreased with sodium bicarbonate compared to NS (32% vs 52%, $P = .043$).
- Subsequent prospectively planned individual patient meta-analysis revealed that alkalinization with sodium bicarbonate infusion was not associated with a lower overall incidence of AKI but reduced severe AKI and the need for KRT in elective CABG.

Perioperative use of RAASi

- Systematic review and meta-analysis conducted in 2018 confirmed insufficient evidence to recommend routine discontinuation of RAASi on the day of surgery.
- However, discontinuation should be considered in patients with hypotension, hyperkalemia, and/or requirement for vasopressors.

Remote ischemic preconditioning (RIPC): 2022 meta-analysis revealed that RIPC reduces AKI incidence (based on AKIN and KDIGO criteria) after cardiac surgery. The renoprotective effect is mainly evident during volatile-only anesthesia and in non–high-risk patients.

Management of high-risk surgical patients

- Key beneficial interventions: hemodynamic monitoring and optimization, avoidance of hypotension and hypoperfusion
- Protocolized use of inotropes to optimize oxygen delivery in late critical illness has not been shown to reduce the incidence of AKI or improve outcomes.

Endovascular aortic aneurysm repair (EVAR) versus open aortic surgery

- EVAR avoids aortic cross-clamp but still requires general anesthesia and aortic manipulation with associated atheroembolic complications.
- Potential problem with EVAR: radiocontrast use, CA-AKI

Combat injury/surgery: Associated rhabdomyolysis increases AKI risk. Aggressive management of rhabdomyolysis is warranted.

Unestablished pharmacologic therapies

Use of erythropoietin (EPO) in AKI

- Experimental models: effective if used within 6 hours of ischemia-reperfusion injury
- Clinical studies: no definitive renoprotective effect shown thus far

Levosimendan

- Calcium-sensitizing agent with inotropic properties
- Use of levosimendan in adults with sepsis or undergoing cardiac surgery has not been shown to be effective in terms of renoprotection or mortality.
- There is no role for the use of levosimendan in critically ill patients based on current data.

Low-dose ANP

- 2019 systematic review and meta-analysis involving 18 randomized controlled trials revealed a significant reduction in KRT requirement and lower ICU and in-hospital stay.
- However, small size and qualities of involved trials render data as "insufficient to conclude efficacy of low-dose ANP" for the prevention or treatment of AKI.

Kidney replacement therapy

Timing of KRT

- Ideal timing for KRT initiation remains unclear and should be individualized based on clinical status and laboratory findings.

- Consider isovolumic FST: Nonresponders predict progression to more severe AKI and likely impending need for KRT.
- Fluid overload at the time of KRT initiation in critically ill patients with AKI may be associated with adverse outcomes.

Dialysis modality selection

- KRT modalities used in the management of AKI include intermittent hemodialysis (iHD), sustained low-efficiency dialysis (SLED), sustained low-efficiency daily dialysis (SLEDD), prolonged intermittent renal replacement therapy (PIKRT), continuous kidney replacement therapy (CKRT), and PD. See **Chapter 12: Continuous Kidney Replacement Therapy** for a more detailed discussion on CKRT.
- Current data suggest no definitive advantage for any KRT modality on short-term kidney or patient survival.
- Current data suggest *no definitive mortality benefit* between iHD versus CKRT. Nonetheless, iHD and prolonged iHD provide faster solute removal than CKRT and are preferred for hyperkalemia, severe metabolic acidosis, and poisoning.
- In terms of CKRT, current data have not demonstrated survival benefit difference between diffusive versus convective mode of clearance (ie, continuous venovenous hemodialysis [CVVHD] vs continuous venovenous hemofiltration [CVVH]).
- KDIGO:
  - Use of CKRT is suggested over intermittent therapies in patients with hemodynamic instability, acute brain injury, or other causes of increased intracranial pressure or generalized cerebral edema.
  - Use iHD, CKRT, or hybrid modalities (eg, PIKRT or SLED) as complementary, not competing, techniques in patients with AKI.
- PD: Single-center studies have suggested the safe use of high-volume PD and tidal PD in selected critically ill patients with AKI. Tidal PD refers to partial drainage of peritoneal fluid with each exchange.

KRT dosing (refer to Appendix A4.5 for definition of Kt/V)

- For iHD: Kt/V greater than 1.2 per treatment 3 times a week is suggested.
- For PD: Kt/V of 0.3 per session is suggested.
- KRT: Effluent volume of 20 to 25 mL/kg/h should be delivered.

Anticoagulation for CKRT

Regional citrate anticoagulation

- KDIGO suggests the use of regional citrate anticoagulation (RCA) over heparin for all patients if there is no contraindication.
- Use RCA instead of heparin for patients with moderate- to high-bleeding risk
- Citrate binds to Ca^{2+} thereby inactivating Ca^{2+}-dependent procoagulants. Most of the calcium citrate complexes formed are removed in the effluent. The remaining calcium citrate is returned to circulation, where citrate undergoes hepatic metabolism to bicarbonate at a 1:3 conversion ratio.
  - Extracorporeal ionized Ca^{2+} concentrations must be below 0.4 mmol/L to achieve adequate regional anticoagulation.
  - Calcium reinfusion into patient via a separate central line is required to reverse the anticoagulant effect.
  - Potential problems with RCA:

- Citrate toxicity may occur if hepatic conversion to bicarbonate is reduced. This may be detected by having an increased total serum calcium to ionized calcium ratio greater than 2.5 (aka increased "Ca^{2+} gap").

Calcium ratio = (total serum Ca^{2+} [mg/dL] × 0.25)/(systemic ionized Ca^{2+} [mmol/L])

The 0.25 factor is to convert mg/dL to mmol/L if Ca^{2+} is measured as mg/dL.
or

Calcium ratio = (total serum Ca^{2+} [mmol/L])/(systemic ionized Ca^{2+} [mmol/L])

If total serum Ca^{2+} is measured in mmol/L.

- Patients with liver failure or shock liver who cannot metabolize citrate to HCO_3^- should not receive RCA.
- Citrate toxicity can result in metabolic alkalosis in patients with good hepatic conversion to HCO_3^-, high anion gap metabolic acidosis in patients with liver failure or shock liver, hypernatremia (Citrate is infused as hypertonic sodium citrate solutions, ranging from 224 to 420 mmol/L.), reduction in ionized Ca^{2+} (The accumulation of citrate leads to the formation of calcium citrate complex which reduces ionized Ca^{2+}.). Hypercalcemia occurs when calcium infusion is increased to correct the low ionized Ca^{2+}.
- Potential benefits of RCA over heparin anticoagulation:
  - Lower bleeding risk than heparin
  - Lower blood, antithrombin III, and platelet transfusion rates
  - Potential anti-inflammatory benefits
  - Long-term outcome is not known.
- Points to remember regarding citrate anticoagulation:
  - Citrate anticoagulation should not be used with slow continuous ultrafiltration (SCUF) because citrate removal is very minimal with SCUF.
  - A lower blood flow should be used with citrate anticoagulation to reduce citrate dose.

No anticoagulation option: Consider in patients with liver failure because they cannot receive either citrate or heparin, the latter due to high-bleeding risk.

Drug dosing

Drug dosing must be carefully discussed with pharmacy, particularly when KRT modality is being changed (eg, switching from CKRT to iHD or vice versa).

Long-term follow-up

KDIGO AKI Guidelines recommend that physicians "evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD" and manage per KDIGO CKD or CKD-at-risk guidelines as appropriate.

ICU NEPHROLOGY

Fluid Management

Volume overload is associated with worse outcomes

- In general, volume overload is thought to delay diagnosis of AKI and has been shown to be associated with worse outcomes.
- Program to Improve Care in Acute Renal Disease (PICARD) trial:
  - Fluid overload was associated with higher mortality at 60 days and hospital discharge.

    - Fluid overload at the time of AKI diagnosis or at peak SCr was NOT associated with favorable renal recovery.
- Finland AKI (FINNAKI) trial: Patients with fluid overload at KRT initiation had an increased risk of 90-day mortality, even after adjusting for disease severity, time of KRT initiation, modality, and sepsis compared to those without fluid overload.
- Intensive Care over Nations study: Higher cumulative fluid administered over the first 72 hours but not the first 24 hours in critically ill patients was associated with increased hazard of death.

Goal-directed fluid therapy (GDFT)

- GDFT targeting cardiac output and other hemodynamic parameters may improve survival and prevent AKI in perioperative patients.
- However, GDFT has not been shown to benefit survival or kidney outcome in septic shock.

Use of diuretics in AKI

- KDIGO recommends not using furosemide to prevent or treat AKI except for the management of volume overload.
- There is no clear benefit with the use of diuretics on kidney function recovery.
- FST may be used in patients with euvolemia to hypervolemia with AKI to predict the risk for severe AKI and need for KRT.

Colloids versus crystalloids

- Theoretical benefit of colloids: Colloids remain intravascularly better than crystalloids, hence lower requirement for high-volume resuscitation and fewer complications with pulmonary and peripheral edema.
- Nonetheless, KDIGO suggests that isotonic crystalloids be used ahead of synthetic and nonsynthetic colloids for intravascular volume expansion in patients at risk or presenting with AKI in the absence of hemorrhagic shock.

Special notes regarding the use of albumin

- Hyperoncotic albumin (20%-25%) appears to be safe and renoprotective in patients with cirrhosis *with* peripheral edema but should probably be avoided in other clinical settings due to the lack of data.
- Risks of albumin:
    - Virus transmission, Creutzfeldt-Jakob disease
    - 4% albumin infusion in patients with traumatic brain injury may be associated with higher mortality.
    - The use of hyperoncotic albumin may be associated with increased AKI risk, particularly in patients with low intravascular hydraulic pressure (ie, hypovolemia).

Balanced solutions versus NS (0.9% NaCl)

- Earlier studies showed kidney and survival benefits with the use of balanced solution compared with NS.
    - The Isotonic Solutions and Major Adverse Renal Events Trial (SMART): Among critically ill adults, the use of balanced crystalloids (n = 7,942) versus NS (n = 7,860) resulted in a lower rate of major adverse kidney event at 30 days (MAKE30), 14.3% versus 15.4%, respectively (P = .04), and trend in improved in-hospital mortality at 30 days, 10.3% versus 11.1%, respectively (P = .06). MAKE30 is defined as a composite of death, new requirement for KRT, or final SCr of 200% or more from baseline at 30 days.

- 2018 Balanced Crystalloids versus Saline in Noncritically Ill Adults trial: Balanced crystalloids had a lower incidence of MAKE30 than NS (OR 0.82; 95% CI, 0.70-1.04, *P* = .01).
- The 2018 Balanced Crystalloids versus Saline in Critically Ill Adults trial: Balanced crystalloids (*n* = 6,708) administered in the emergency department resulted in a lower incidence of MAKE30 than NS (*n* = 6,639) infusion in the emergency department, 4.7% versus 5.6%, adjusted OR 0.82, *P* = .01. There was no difference in hospital-free days between the two groups.

- Later studies did not show kidney or survival benefits of using balanced solution over NS.
  - 2021 BaSICS randomized clinical trial: Among critically ill patients (*n* = 11,052) requiring fluid challenges, the use of a balanced solution compared with NS did not significantly reduce 90-day mortality.
  - 2022 PLUS double-blind, randomized, controlled trial: Among critically ill patients (*n* = 5,037) recruited from 53 ICUs in Australia and New Zealand, the risks of death (21.8% vs 22.0%, *P* = .09) and AKI (rise in SCr of 0.41 ± 1.06 mg/dL vs 0.41 ± 1.02 mg/dL, *P* = NS) were not different between balanced solution compared with NS, respectively. KRT requirement rates were also similar between the two groups.

Transfusion in nonhemorrhagic critically ill patients

RBC transfusion

- Stored RBC membrane injuries: carbohydrate loss, oxidative injuries, potassium leakage; altered oxygen affinity and delivery; increased RBC adhesions to endothelial cells
- Safety of aged versus fresh blood transfusions: The storage age of RBCs does not affect patient mortality or AKI event rates based on current data.
- Recommended indications:
  - Hb of 7 g/dL or less for patients without cardiac disease
  - Hb less than 7 to 8 g/dL in patients with coronary artery disease
  - Transfusions for higher Hb if symptomatic in euvolemic patients (eg, cardiac chest pain, congestive heart failure, unexplained tachycardia, or hypotension not responsive to fluid replacement)

Platelet transfusion

- Most bleeding occurred at a platelet count of less than 7,000/μL.
- Transfuse platelets if the count is less than 10,000/μL.
- Prophylactic transfusion for invasive procedures: poor data; current expert opinion suggests transfusion platelets if the count is less than 50,000/μL.
- For central nervous system (CNS) injury, multisystem trauma, neurosurgery: Transfuse platelets if the count is less than 100,000/μL.
- In patients requiring massive blood transfusion (more than 10 units of packed RBCs within 24 hours), transfuse in a 1:1:1 ratio of RBCs, plasma, and single-donor platelets.

Plasma transfusion, FFP

- Contains albumin, coagulation factors, fibrinolytic proteins, and immunoglobulins
- May be given for patients with coagulopathy and active or anticipated bleeding
- FFP may not correct an INR of 1.85 or less.
- Plasma transfusion is associated with an increased risk for lung injury and trend toward increased mortality. FFP should not be used for the sole purpose of a plasma expander.

Complications associated with transfusions of blood products

- Volume overload, hyperkalemia

- Blood transfusion reactions ranging from generalized discomfort, skin rash, fevers, tachycardia, and hypotension, to anaphylactic reaction. The development of blood transfusion reactions may be associated with an increased risk of AKI.
- Transfusion-related acute lung injury (TRALI):
  - TRALI: new-onset acute lung injury within 6 hours of receiving a plasma-containing blood component in the absence of other causes of acute lung injury
  - Incidence: up to 1 in 20 patients
  - Risks:
    - Recipient factors: high interleukin-8 (IL-8) levels, high peak airway pressures (eg, >30 cm H_2O), shock, tobacco and alcohol abuse, positive fluid balance
    - Blood product factors: plasma-rich products, increased antihuman leukocyte antigen class II antibodies and antihuman neutrophil antibodies, blood from female donors
- Transfusion-related immunomodulation (TRIM):
  - Immunosuppressive effect on recipients from donor antigens
  - Increased risk of malignancy recurrence and hospital-acquired infection

Vasopressors

Indication for vasopressors

- End-organ dysfunction due to vasodilatory shock not responding to volume resuscitation (ie, fall in baseline SBP by >30 mm Hg, or MAP is below 60 mm Hg)
- KDIGO 2012:
  - The use of vasopressors in conjunction with fluids is recommended for patients with vasomotor shock who are at risk for AKI.
  - Target MAP of 65 to 90 mm Hg depending on age, chronic (baseline) BP, or other comorbidities.
  - More research is needed.

General recommendations

- Norepinephrine is the first-line vasopressor, followed by vasopressin or epinephrine.
- Dopamine is only recommended for patients with bradycardia who have been highly selected.

Types of vasoactive agents (see **Tables 11.5 and 11.6**)

Table 11.5 Clinical effects of receptor stimulation by agonists

Receptor	Clinical effects with receptor stimulation
α1	• Vasoconstriction • Smooth muscle contraction
α2	• Norepinephrine (noradrenaline) inhibition • Mixed effects on smooth muscle • Platelet activation
β1	Positive chronotropic and inotropic effects
β2	• Smooth muscle relaxation • Glycolysis (Side effect of hyperlactatemia is possible with use of β2 agonists.)
AVPR1a	• Vasoconstriction

Receptor	Clinical effects with receptor stimulation
	• Increased aldosterone synthesis and vasopressin release
AVPR1b	Adrenocorticotropin hormone (ACTH) release
AVPR2	Antidiuresis
ATR1	• Vasoconstriction • Increased aldosterone synthesis and vasopressin release (ATR1 may be downregulated in sepsis.)
ATR2	Vasodilation
DA1	Vasodilation in cerebral, coronary, renal, and mesenteric vascular beds
DA2	Cognitive function

Abbreviations: ATR, angiotensin receptor; AVPR, arginine vasopressin receptor; DA, dopamine receptor.

Table 11.6 Commonly used vasoactive and inotropic agents

Agent	Receptor activity	Comments
Norepinephrine (NE)	α1, α2 Less potent on β1, β2	• First-line vasopressor for septic shock • Vasoconstriction; some positive inotropic activity (increased ventricular contractility)
Vasopressin	AVPR1a, AVPR1b, AVPR2	• Add-on vasopressor • May potentially depress cardiac function and precipitate ischemia in patients with coronary artery disease • When both NE and vasopressin are used, NE should be weaned first due to potential hemodynamic instability (rebound hypotension) if vasopressin is weaned first.
Epinephrine	Similar to NE except for more β1-agonism	• Add-on vasopressor in septic shock • First-line vasopressor for anaphylactic shock • Comparable in efficacy as NE but with increased risk of splanchnic vasoconstriction (thus ischemia), tachyarrhythmias, hyperlactatemia
Phenylephrine	Nearly pure α1-agonist	• Can cause reflex bradycardia • May be considered as an alternative vasopressor when tachyarrhythmias preclude the use of NE, epinephrine, or dopamine • May reduce stroke volume and cardiac output in patients with cardiac dysfunction • Phenylephrine was associated with higher mortality than NE use.
Dopamine (DA)	α 1, β1 DA1, DA2	• Receptor selectivity is dose dependent: Low dose acts on DA, moderate dose acts on β1, and high dose acts on α1 receptors. • May be considered as an alternative vasopressor in highly selective patients with bradycardia and low risk for tachyarrhythmias • Lower efficacy as a vasopressor and greater adverse effects (ie, tachyarrhythmias) compared with NE • Although low-dose dopamine in preclinical and small trials suggested splanchnic and renal vasodilation, subsequent RCT did not show any renal or survival benefits.
Angiotensin II	ATR1, ATR2	• May be used in early resuscitation for patients with profound hypotension • May increase glomerular filtration rate due to increased efferent arteriolar vasoconstriction

Agent	Receptor activity	Comments
		• More data are needed.
Dobutamine	Inotropic agent	• Increases cardiac contractility and heart rate but may cause hypotension and tachyarrhythmias • First-line vasopressor for cardiogenic shock with low cardiac output • May be used as add-on therapy to NE and vasopressin to improve cardiac output from sepsis-induced depressed ventricular function (at the expense of tachyarrhythmias and increased myocardial consumption)
Milrinone	Inotropic agent	• Increases cardiac contractility and heart rate • Alternative inotropic agent to improve cardiac output in cardiogenic shock not responsive to other agents • May cause systemic vasodilation, hypotension, and ventricular arrhythmias • Milrinone has greater vasodilating action compared with dobutamine.

Abbreviations: ATR, angiotensin receptor; AVPR, arginine vasopressin receptor; RCT, randomized controlled trial.

- Special considerations regarding the use of vasoactive agents:
  - Optimize fluid status PRIOR to the use of vasopressors (eg, pulmonary capillary wedge pressures of 18-24 mm Hg for cardiogenic shock, and 12-14 mm Hg for septic or hypovolemic shock before consideration for use of vasopressors).
  - Avoid excessive rise in systemic vascular resistance (SVR), hence cardiac workload, in patients with poor cardiac function (eg, keep SVR 700-1,000 dynes × s/cm^5).
  - Absorption of subcutaneous medications (eg, heparin, insulin) may be reduced due to peripheral vasoconstriction.
  - Dopamine: Clinical effects are dose dependent.
    - Low dose (1-2 µg/kg/min): predominantly vasodilates cerebral, coronary, renal, and mesenteric vascular beds via dopamine-1 receptors
    - Intermediate dose (2-5 µg/kg/min): mix of vasodilation + increased stroke volume (SV) + some degree of α-adrenergic receptor activation; overall net effect may be seen as increased MAP.
    - High dose (5-10 µg/kg/min): increases SV, cardiac output; variable chronotropic effect via β-1 adrenergic stimulation
    - Very high dose of greater than 10 µg/kg/min: predominantly vasoconstrictive via α-1 receptors
    - Caution: dysrhythmias with doses higher than 2 µg/kg/min

Special uses of vasoconstrictors

- Hyperdynamic septic shock (distributive shock):
  - First line: norepinephrine (levophed, norepinephrine [NE] acts on both α-1 and α-2 receptors to cause vasoconstriction and some increase in cardiac contractility, thus cardiac output; less effect on β1 and β2)
  - Alternative/second-line agents:
    - Epinephrine (acts on α-1 receptor to cause vasoconstriction, thus increasing MAP via increasing SVR, without altering cardiac inotropy or chronotropy); useful in patients with hypotension (eg, hyperdynamic sepsis, neurologic or anesthesia related hemodynamic instability, with SVR <700 dyes × s/cm^5); contraindicated if SVR is greater than 1,200 dynes × s/cm^5
    - Vasopressin: may be added early to NE therapy rather than monotherapy with NE to minimize NE-related adverse effects (eg, tachyarrhythmias with high-dose monotherapy

NE). In cardiac arrest, vasopressin has not been shown to be beneficial. Current guidelines advise against its use.

- Third-line agent:
  - Angiotensin II (Ang II): U.S. Food and Drug Administration (FDA) approved the use of Ang II in patients with distributive shock, predominantly septic shock in 12/2017. The use of Ang II may incur increased risk of DVT. DVT prophylaxis while on Ang II is recommended. Survival benefit is questioned.
  - Phenylephrine (Neosynephrine, nearly pure α-1 agonist) may reduce SV and should be a last resort option. Phenylephrine may cause reflex bradycardia and may be considered in patients with β-adrenergic-associated tachyarrhythmias.

- Hypodynamic shock (eg, neurologic or anesthesia related): first line: norepinephrine
- Anaphylactic shock, hypotension following CABG:
  - Epinephrine (adrenalin: potent β-1 adrenergic receptor activity and moderate β-2 and α-1 adrenergic receptor effects; at high dose, predominant effects include increased cardiac output and SVR)
  - Epinephrine may be considered as second-line agent for patients with septic shock (who failed NE).
  - Considerations: dysrhythmias and splanchnic vasoconstriction
- Cardiogenic shock:
  - First line: norepinephrine
  - *Once adequate perfusion pressure has been achieved*, dobutamine may be added as safely tolerated. Dobutamine acts predominantly on β-1 adrenergic receptor, thus leading to increased inotropy and chronotropy to reduce left ventricular filling pressure and improve cardiac output. There may be an overall slight reduction in BP as a reflex response to the increased cardiac output.
  - Dobutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.
- Bradycardia-induced hypotension: Isoproterenol acts on β-1 adrenergic receptors to produce a prominent chronotropic effect.

Complications of vasopressor therapy

- Tissue hypoperfusion (eg, blue distal extremities, skin necrosis, bowel ischemia, reduced kidney perfusion, myocardial ischemia). For skin necrosis due to IV infiltration, consider local subcutaneous injection with phenolamine (5-10 mg in 10 mL NS).
- Dysrhythmias (eg, tachycardia, atrial fibrillation, reentrant atrioventricular node tachycardia, or ventricular tachyarrhythmias; seen with agents with potent chronotropic effects via β-1 receptor stimulation)
- Electrolyte disturbances (hyponatremia with vasopressin, hypokalemia with agents with potent β2-receptor agonistic effects such as dobutamine and isoproterenol, propensity for hyperkalemia is possible with agents with strong α-adrenergic activity such as phenylephrine and norepinephrine)
- Hyperglycemia (particularly with NE and epinephrine)

HEMODYNAMIC MONITORING

Table 11.7 summarizes common hemodynamic monitoring procedures along with their clinical utility and limitations.

Table 11.7 Common hemodynamic monitoring procedures

Procedures	Comments
Clinical examination	Increased capillary refill and cold clammy skin are consistent with low cardiac output.
Diastolic blood pressure (DBP)	Low DBP suggests low vascular tone (eg, sepsis) or marked volume depletion.
Arterial pulse pressure (PP)	Low PP suggests low stroke volume (eg, poor ejection fraction, aortic regurgitation, severe hypovolemia).
Passive leg raising	Clinical utility: • Assess hemodynamic differences with head of bed tilting at 45° up and 45° down. • May provide information on fluid responsiveness Limitations: contraindicated in patients with high intracranial pressure or lower extremity amputations or patients who cannot lie flat
Echocardiogram	Clinical utility: • Assess cardiac structure and function. • Assess volume status based on inferior vena cava size and collapsibility. Limitation: no continuous hemodynamic monitoring
Central venous pressure	Clinical utility: • Assess volume status, CVP, $ScvO_2$, $PcvCO_2$, right-sided heart failure. • Assess organ perfusion pressure = MAP − CVP. Limitation: does not predict fluid responsiveness
Pulmonary artery catheterization	Clinical utility: • Indicated in patients with refractory shock associated with right ventricular dysfunction and/or with ARDS Limitation: invasive; cannot provide accurate short-term changes in cardiac output due to its noncontinuous monitoring of cardiac output
Arterial line	Clinical utility: • Assess arterial BP, PPV, SVV. Limitation to PPV and SVV assessments: only reliable during mechanical ventilation with a tidal volume of ≥8 mL/kg in sedated patients (without spontaneous breathing activity) and without cardiac arrhythmias
Transpulmonary thermodilution	Clinical utility: • Assess CO, PPV, SVV, global end-diastolic volume (preload), cardiac function index, global ejection fraction, extravascular lung water (pulmonary edema), pulmonary vascular permeability index (pulmonary capillary leak). Limitation: requires a central venous catheter and a thermistor inserted into the femoral artery

Abbreviations: ARDS, acute respiratory distress syndrome; BP, blood pressure; CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; $PcvCO_2$, CO_2 pressure in central vein; PP, pulse pressure; PPV, pulse pressure variation; $ScvO_2$, oxygen saturation in central vein; SVV, stroke volume variation.

Static Testing for Fluid Responsiveness

Static testing options

Central venous pressure via central line (internal jugular or subclavian vein): estimates right atrial pressure, and in effect, right ventricular end-diastolic volume, blood volume, and right ventricular preload

Pulmonary arterial occlusion pressure (PAoP) via pulmonary artery (PA) catheter: estimates left atrial pressure, and in effect, left ventricular diastolic volume

Left ventricular end-diastolic area (LVEDA) via transthoracic or transesophageal echocardiography: Theoretically, an increase in LVEDA corresponds to greater ventricular

myocardial stretch, thus presumed greater cardiac output.
End-expiratory occlusion with echocardiography: This technique involves holding the patient at end-expiration for approximately 15 seconds. A rise in SV suggests fluid responsiveness.

Limitations to static testing

- CVP, PAoP, and LVEDA lack accuracy and precision.
- CVP: invasive, falsely high readings with pulmonary HTN, right ventricular dysfunction, or high PEEP
- PAoP: invasive, falsely high readings with acute respiratory distress syndrome (ARDS) due to misleadingly high cardiac filling pressure
- LVEDA: cannot predict where in the Frank-Starling curve the myocardial stretch is to accurately determine actual cardiac output

Dynamic Testing for Fluid Responsiveness

Pulse pressure variation (PPV) and stroke volume variation (SVV)

- The technique is based on the principle of pulsus paradoxus, which is the variation of SV and BP with respiration. Positive pressure ventilation causes decreased venous return and increased right ventricular afterload, hence reduced SV or pulse pressure (PP). Volume depletion exaggerates SVV and PPV.
- PPV and SVV measurements require that the patient is sedated without spontaneous breathing or arrhythmia and mechanically ventilated with tidal volume 8 mL/kg or more.

$$\textbf{PPV} = 100 \times (\text{PP[highest value]} - \text{PP[lowest value]})/\text{PP(mean value)}.$$

Variation of greater than 12% suggests greater likelihood for fluid responsiveness.

$$\textbf{SVV} = 100 \times (\text{SV[highest value]} - \text{SV[lowest value]})/\text{SV(mean value)}.$$

Variation of greater than 12% suggests greater likelihood for fluid responsiveness.

IVC diameter

- An IVC diameter of smaller than 10 mm suggests that fluid is tolerated.
- Subcostal measurement of IVC diameter (below junction with right atrium) changes during respiration by echocardiography: A change of greater than 10% to 18% in IVC diameter between inspiration and expiration (expiration is considered as "baseline") predicts fluid responsiveness with sensitivity 50% to 100% and specificity 53% to 100%. This test may be used for both ventilated and spontaneously breathing patients.

Passive leg raising

- Measures change in various hemodynamic parameters between tilting the head of bed down to 45° versus head of bed up at 45%. Tilting of bed is preferred over leg bending to avoid compression of femoral veins.
- Changes in cardiac output, PP/SV, MAP, or PA occlusion pressure may be measured. Improvement in hemodynamic parameters of greater than 10% have been suggested to predict fluid responsiveness. This test is limited to patients who can lie flat and is contraindicated in patients with high intracranial pressure or severe peripheral vascular disease.

Hemodynamic Methods for Measuring Cardiac Output and Body Volume Status

Thermodilution: requires a PA catheter, where a small volume of cold solution (injectate) is injected into the PA catheter. The change in blood temperature following blood mixing with the injectate can be used to calculate cardiac output.

Transpulmonary thermodilution: theory as above. Injectate is injected through a standard central venous catheter and a thermistor which is inserted into the femoral artery. This method is thought to be less invasive compared to the thermodilution technique above.

Esophageal Doppler

- Doppler is positioned in the esophagus to measure aortic diameter and velocity of blood flow through the aorta, where cardiac output is estimated by the equation: velocity = flow/cross-sectional area. Flow (blood flow) reflects cardiac output.
- Limitations: Measurements may be affected by flow turbulence (eg, from aneurysm, atherosclerotic disease) and by upward flow from the aortic arch (Blood volume that does not reach the aortic area of interest leads to falsely low cardiac output.).
- Good correlation with thermodilution method

Thoracic electrical bioimpedance (TEB)

- Technique is based on Ohm law: Voltage = Current × Resistance.
- Measures electrical resistance on an applied current, where the resistance is affected by the relative water content in the descending aorta, that is, amount of blood flow through the aorta. A volume-repleted patient will theoretically have a low TEB (ie, low resistance) compared with that of a volume-depleted patient.

Pulse contour analysis: measures/calculates cardiac performance based on variations in arterial line tracings with bedside computers/programs.

Pulse oximetry waveform variation: The pulse oximetry curve represents the amount of infrared light absorbed by circulating Hb during a cardiac cycle. Variation in the amplitude of this curve relates to the amount of blood in the capillary bed/volume status.

Ethics and Palliative Care

Goals of palliative care in end of life

- Reduce patient's symptom burden.
- Reduce caregiver burden.
- Provide emotional and spiritual support for all involved.

Palliative care

- Palliative care is underutilized in patients with AKI requiring KRT compared to those with other diagnoses despite having comparable or higher mortality.
- Current data suggest that palliative care is offered less frequently among African Americans and Hispanics compared with Caucasians, less frequently among rural than urban teaching hospitals, and less frequently in the Northeast compared with Southern, followed by a Western region of the United States.
- Factors to consider in providing palliative care/end-of-life care:
  - Patient's characteristics and medical conditions: age, comorbidities, functional status, nutritional status, decision-making capacity

- Present illness: severity of disease and expected progression
- Patient's wishes if applicable, otherwise designated/appointed decision maker
- Prognosis: possibility of getting discharged
- KRT complication risks: hemodynamic instability, cardiac arrest
- Limited-time KRT trial may be considered and discussed with all involved including health care professionals, family, and patient. Discussion and documentation of expected goals for KRT continuation or discontinuation should be done before KRT initiation.

CHAPTER 12

Continuous Kidney Replacement Therapy

Ashita J. Tolwani

BACKGROUND

- Continuous kidney replacement therapy (CKRT) is preferable for patients who are hemodynamically unstable, offering better volume management than intermittent hemodialysis (iHD) in critically ill patients with acute kidney injury (AKI).
- CKRT enhances hemodynamic stability by removing volume and solutes more gradually than iHD.
- Observational studies suggest improved renal recovery with CKRT over iHD, although randomized controlled trials (RCTs) have not confirmed this.
- RCTs have not shown a survival advantage with CKRT compared to iHD.

Patient selection

CKRT is the preferred kidney replacement modality for patients with AKI/kidney failure who have hemodynamic instability, particularly when steady metabolic and volume control is necessary.

Indications for CKRT

- All the traditional indications for kidney replacement therapy (KRT) apply to patients with hemodynamic instability and/or multiorgan failure.

- AKI conditions requiring continuous solute control such as severe rhabdomyolysis and tumor lysis syndrome
- AKI complicated by acute brain injury, acute liver failure, or cardiopulmonary failure requiring extracorporeal membrane oxygenation (ECMO)
- AKI conditions requiring slow correction of severe dysnatremias
- Patients with AKI with high risk of osmotic disequilibrium with iHD

Advantages

- Provides superior volume control, essential for patients with cardiac and/or pulmonary failure
- Preferred for patients at risk for or with intracranial hypertension due to its gradual solute removal and decreased osmotic shifts
- Offers higher total daily clearance compared to standard iHD, allowing full-dose nutrition without restrictions

Disadvantages

- Requires ICU-level care
- Provides slower toxin/solute removal, limiting its use in patients with severe hyperkalemia or drug intoxications
- Restricts patient mobility
- Often requires anticoagulation
- Increases risk of hypothermia
- Increases nutritional losses
- Increases drug clearance, which complicates medication dosing
- Increases costs

Timing of KRT: Early Versus Late Initiation

- There is a general consensus that KRT should be considered in patients with AKI and medically refractory complications such as severe hyperkalemia, severe metabolic acidosis, fluid overload

resistant to diuretic therapy, signs of uremia, and specific drug intoxications.

- Recent RCTs on the timing of KRT initiation based on an earlier AKI stage (AKI stage 2 or 3) have shown mixed results, with the ELAIN (Early Versus Late Initiation of Dialysis in Acute Kidney Injury) trial indicating benefits of early renal replacement therapy (RRT) on mortality, while AKIKI (Initiation of Renal Replacement Therapy in Acute Kidney Injury), IDEAL-ICU (Initiating Dialysis Early Versus Delayed in the Intensive Care Unit), and STARRT-AKI (Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury) trials found no advantage.
- STARRT-AKI, the largest multinational trial with 2,927 patients, found no significant difference in 90-day mortality but observed higher rates of KRT dependency and adverse events in the early initiation group.
- AKIKI2 explored delayed versus more-delayed KRT initiation, showing no significant difference in outcomes but a potential risk with excessive delay.

NOTE

Existing RCTs suggest that starting KRT immediately at AKI stage 2 or 3, without an urgent indication, does not significantly improve patient outcomes and introduces significant risks. There is a need for more comprehensive data to define clear criteria for initiating KRT in cases of persistent AKI.

CKRT Procedure

Determinants of the CKRT prescription include modality, dose, hemofilter selection, blood flow, anticoagulation, and fluid removal goals.

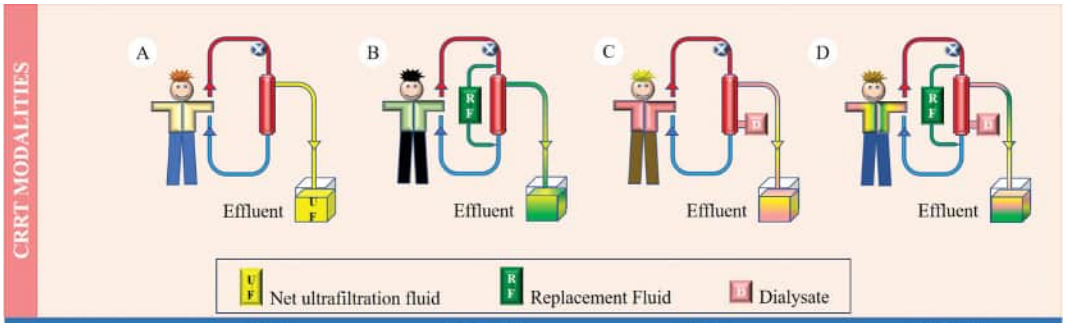
Modalities of CKRT

CKRT modalities for clearance include convective (CVVH [continuous venovenous hemofiltration]), diffusive (CVVHD [continuous venovenous hemodialysis]), or combined (CVVHDF [continuous

venovenous hemodiafiltration]) methods for solute clearance, with no clear evidence favoring one over the others in terms of patient outcomes.

Solute clearance methods

Figure 12.1 illustrates the different CKRT modalities.



	A. SCUF	B. CVVH	C. CVVHD	CVVHDF
Goal	Fluid removal only	Combined solute & fluid removal		
Force of solute clearance	No solute clearance	Convection	Diffusion	Diffusion & Convection
Operative fluid	None	Pre/Post Replacement Fluid	Dialysate	Dialysate & Replacement Fluid
Effluent	Fluid Removed	Fluid Removed + Replacement Fluid	Fluid Removed + Dialysate	Fluid Removed + Replacement Fluid + Dialysate

FIGURE 12.1 Continuous kidney replacement therapy modalities. Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; SCUF, slow continuous ultrafiltration.

Continuous venovenous hemofiltration focuses on removing small to middle-sized molecules through convection, utilizing replacement fluid (RF).

Continuous venovenous hemodialysis achieves small solute removal primarily through diffusion, using dialysate. However, the use of high-flux dialyzers allows for convective flow via filtration and backfiltration between the dialysate and blood compartments as the result of pressure gradient changes along the length of the membrane.

Continuous venovenous hemodiafiltration combines both techniques for comprehensive solute clearance, employing both

dialysate and RF.

NOTE

Despite theoretical benefits, convective removal of middle-sized molecules has not demonstrated clinical advantages in clinical trials.

Placement of RF in CVVH/CVVHDF:

- RF in CVVH/CVVHDF can be administered prefilter, postfilter, or both to optimize clearance and minimize filter clotting risks by keeping the filtration fraction (FF) at 20% to 25% or less.
- FF is the proportion of plasma water entering the filter that is removed by ultrafiltration and is inversely proportional to blood flow rate.

Infusing RF postfilter into the venous line limits the ultrafiltration rate due to hemoconcentration with increased FF but ensures direct correlation of clearance with the ultrafiltration rate.
Infusing RF prefilter into the arterial line dilutes the concentration of solutes entering the hemofilter and reduces overall clearance, but prolongs circuit life by decreasing FF.

Other CKRT modalities

Slow continuous ultrafiltration (SCUF) is utilized for primarily removing plasma water with minimal solute clearance.
High volume hemofiltration (HVHF) with ultrafiltration/effluent rates exceeding 50 mL/kg/h is theorized to provide benefit in sepsis by removing cytokines. However, RCTs have not demonstrated improved survival rates and suggest potential adverse effects from the loss of vital nutrients, anti-inflammatory cytokines, and antibiotics.

CKRT dose

- The clearance of urea and other low-molecular-weight solutes in CKRT is approximately equal to effluent flow rate, which is a

surrogate of dose and reported in mL/kg/h.

- The primary determinant of clearance in CKRT is the total effluent rate rather than blood flow rate.
- Two major RCTs, the ATN (Acute Renal Failure Trial Network) and RENAL (Randomized Evaluation of Normal Versus Augmented Level of Replacement Therapy) studies, compared high (35-40 mL/kg/h) versus low (20-25 mL/kg/h) dose CKRT in over 2,000 patients with AKI in the ICU, finding no mortality or kidney recovery benefit from higher doses.
- KDIGO (Kidney Disease: Improving Global Outcomes) recommends a 20 to 25 mL/kg/h effluent rate, though actual delivered doses can be up to 20% lower due to treatment interruptions.
- To compensate for "downtime," a prescribed rate of 25 to 30 mL/kg/h is suggested by KDIGO.
- Higher CKRT doses may be temporarily necessary for conditions such as hyperkalemia, severe acidosis, or hyperammonemia; once solute control is achieved, doses should be adjusted back to standard ranges.
- CKRT dosing must be flexible and continually tailored to the evolving requirements of critically ill patients.

NOTE

Existing RCTs have not demonstrated improved survival rates with HVHF (ultrafiltration/effluent rates >50 mL/kg/h) or high dose CKRT (35-40 mL/kg/h vs 20-25 mL/kg/h).

Selecting hemofilters

- CKRT utilizes high-permeability, high-flux membranes such as polyacrylonitrile (AN69), polyarylethersulfone (PAES), and polyethersulfone (PES), with no single type proven superior.
- Polyacrylonitrile membranes, noted for their negative charge, may enhance the removal of certain solutes by adsorption but require

caution in patients on angiotensin-converting enzyme (ACE) inhibitors due to the risk of bradykinin release.

Blood flow rates

Table 12.1 summarizes main points for blood flow rates for different CKRT modalities.

Table 12.1 Recommended blood flow rate based on CKRT modalities and use of regional citrate anticoagulation

	Dialysate flow	Convective flow	Blood flow
Routine CKRT prescription	20-25 mL/kg/h (diffusion, convection, or both)		100-300 mL/min
Diffusion-based CKRT	20-25 mL/kg/h	None	≥2.5 times dialysate flow
Convection-based CKRT Prefilter replacement fluid	None	20-25 mL/kg/h Prefilter RF	≥6 times prefilter flow rate
Convection-based CKRT Postfilter replacement fluid	None	20-25 mL/kg/h Postfilter RF	≥5 times postfilter flow rate
Citrate anticoagulation	20-25 mL/kg/h		<150 mL/min is recommended to reduce the systemic effects of citrate.

Abbreviations: CKRT, continuous renal replacement therapy; RF, replacement fluid.

- Blood flow rate in CKRT is prescribed typically in the range of 100 to 300 mL/min.
- Unlike iHD, small solute clearance in CKRT is minimally affected by changes in blood flow rate, and dose is directly proportional to effluent rate.

- However, at very high CKRT doses, blood flow may begin to significantly influence clearance.
- For diffusion-based CKRT modalities, the blood flow rate should be at least 2.5 times the dialysate rate to allow for near-complete saturation of the dialysate.
- For convective-based CKRT modalities, the greater the prefilter RF rate relative to blood flow rate, the larger the loss of efficiency of solute clearance compared to postfilter RF at the same rate due to the predilution effect. Therefore, when using prefilter RF, a minimum blood flow rate of 200 to 250 mL/min (or at least 6 times the prefilter RF rate) is recommended to decrease the dilution effect of prefilter RF on clearance.
- In contrast, high postfilter RF rates increase the FF and clotting. Therefore, blood flow rates below 100 to 150 mL/min may heighten the risk of clotting by causing blood stasis and a higher FF due to the inverse relationship between FF and blood flow. When using postfilter RF, the FF should be kept below 0.25 to avoid clotting of the hemofilter (ie, blood flow rate should be at least 5 times the RF rate).
- When utilizing citrate anticoagulation, blood flow rates below 150 mL/min are recommended to reduce the systemic effects of citrate.

  Hemodynamic stability is unaffected by blood flow rate changes, given the constant blood volume in the circuit.

  NOTE

Ultrafiltration

- Guidance on prescribing volume removal in CKRT is scarce.
- Managing volume in CKRT requires combining various data and continual reassessment of ultrafiltration goals, ideally with nephrology and critical care collaboration.
- Net ultrafiltration should be prescribed weight based (mL/kg/h).
- Observational data show a U-shaped relationship between net ultrafiltration and mortality, with 1.0 to 1.75 mL/kg/h associated

with lowest mortality, needing further research for confirmation.

Anticoagulation

Most common options include no anticoagulation, heparin, or citrate, with citrate offering advantages including higher filter life and reduced bleeding complications.

Citrate

KDIGO 2012 AKI guidelines recommend regional citrate anticoagulation (RCA) over heparin for CKRT, except when contraindicated.

RCA procedure (Figure 12.2)

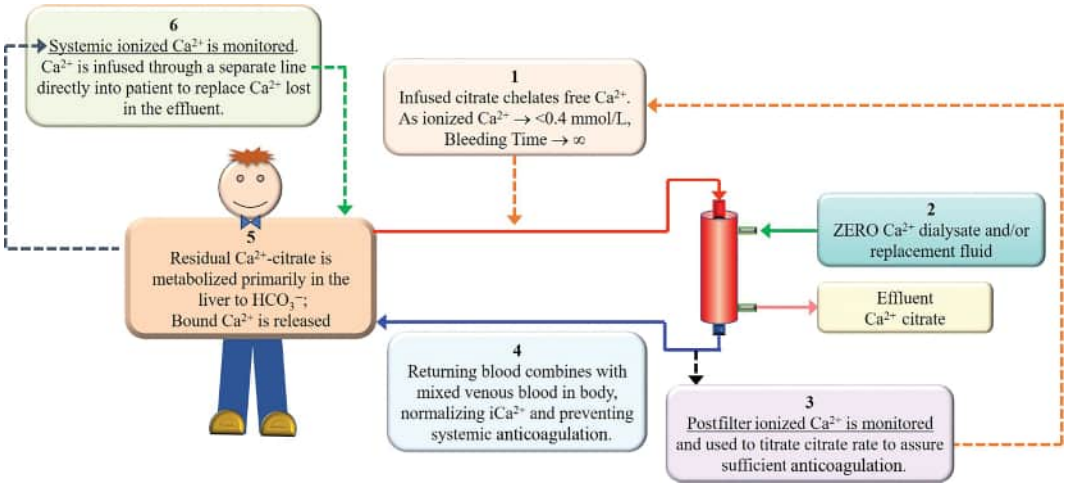

6
Systemic ionized Ca^{2+} is monitored. Ca^{2+} is infused through a separate line directly into patient to replace Ca^{2+} lost in the effluent.
1
Infused citrate chelates free Ca^{2+}. As ionized $Ca^{2+} \rightarrow$ <0.4 mmol/L, Bleeding Time $\rightarrow \infty$
2
ZERO Ca^{2+} dialysate and/or replacement fluid
Effluent Ca^{2+} citrate
5
Residual Ca^{2+}-citrate is metabolized primarily in the liver to HCO_3^-; Bound Ca^{2+} is released
4
Returning blood combines with mixed venous blood in body, normalizing iCa^{2+} and preventing systemic anticoagulation.
3
Postfilter ionized Ca^{2+} is monitored and used to titrate citrate rate to assure sufficient anticoagulation.

FIGURE 12.2 Regional citrate anticoagulation during continuous kidney replacement therapy. 1. The infused citrate chelates free ionized calcium (iCa^{2+}) in arterial blood. As iCa^{2+} reaches a level below 0.4 mmol/L, coagulation of blood can no longer happen (ie, bleeding time reaches "infinity"). This serves to prevent clotting of the dialyzer. 2. Arterial blood undergoes clearance against a zero-calcium dialysate and/or replacement fluid. Most Ca^{2+} citrate complexes formed are cleared into the effluent. 3. Residual iCa^{2+} is measured from the venous port to guide adjustment of the amount of citrate infused in step 1. Goal iCa^{2+} is less than 0.4 mmol/L. 4. Clean blood is returned via the venous line. 5. Any residual citrate in the form of Ca^{2+} citrate is metabolized in the liver to HCO_3^-. The bound Ca^{2+} is released into circulation. 6. Peripheral total calcium and iCa^{2+} are monitored and repleted as needed via a separate line.

- Citrate chelates ionized calcium (iCa) in the extracorporeal circuit. Optimal anticoagulation is achieved when hemofilter iCa is less than 0.4 mmol/L.
- A portion of the calcium citrate complex is lost across the hemofilter while the rest enters the systemic circulation where the liver metabolizes citrate to bicarbonate and calcium is released into circulation.
- Calcium is infused into the patient to replace the calcium lost across the hemofilter.

Potential complications of RCA

- Managing RCA involves monitoring for metabolic alkalosis, metabolic acidosis, calcium imbalances, and hypomagnesemia. Metabolic acidosis may manifest in patients with impaired metabolism of citrate to bicarbonate because the content of bicarbonate in dialysate or replacement fluid is typically low due to the assumption that citrate in these fluids can be metabolized to bicarbonate.
- Patients with severe shock liver and lactic acidosis may not effectively metabolize citrate, resulting in citrate accumulation.
- Citrate accumulation is characterized by low systemic iCa, elevated total calcium, total calcium to systemic iCa ratio of greater than 2.5, anion gap metabolic acidosis, and escalating calcium infusion requirements.
- Despite potential issues, RCA is considered safe even in patients with advanced liver disease and during liver transplants.

Vascular Access

- KDIGO 2012 AKI guidelines advise prioritizing the right internal jugular (IJ) vein for temporary dialysis catheter placement, then femoral or left IJ vein, avoiding subclavian veins unless necessary.
- Proper catheter insertion depth is critical: 15 to 20 cm for right IJ, 20 to 24 cm for left IJ (with tips at the cavoatrial junction), and 20 to 25 cm for femoral catheters (tips in the inferior vena cava).

- Ultrasound guidance and aseptic technique are advised to reduce complications.
- While needle cannulation of arteriovenous fistulae or grafts for CKRT in patients with end-stage kidney disease (ESKD) has been reported, catheters remain the standard to avoid potential complications such as needle dislodgement or damage to the fistulae/grafts caused by prolonged cannulation.

Complications of CKRT

- CKRT complications include vascular access dysfunction, air embolization, complications from anticoagulation, and rare allergic reactions to hemofilters.
- Hypotension during CKRT is influenced by both modifiable (ultrafiltration rate) and nonmodifiable factors (vascular permeability).
- Hypophosphatemia from CKRT, especially with phosphate-free solutions, is linked to adverse outcomes such as prolonged mechanical ventilation due to respiratory muscle weakness.
  - Managing hypophosphatemia involves proactive repletion or using phosphate-containing CKRT solutions, which has shown benefits in reducing hypophosphatemia and mechanical ventilation duration.
  - Commercially available phosphate-containing CKRT solutions lack dextrose, requiring careful monitoring to avoid hypoglycemia and potential euglycemic ketoacidosis.
- Quality assurance and multidisciplinary communication are crucial to prevent complications, requiring local protocols for frequent monitoring and early complication detection.

APPENDIX A: Facts, Formulas, and Protocols Beyond the ABIM Board Exam

CHAPTER 1: SODIUM AND WATER ABNORMALITIES

A1.1 Protocol for Water Loading Test

- Purpose: Water loading test may be used in equivocal cases of SIADH (syndrome of inappropriate secretion of antidiuretic hormone). This test should only be performed in patients with mild hyponatremia and NOT in moderate or severe hyponatremia.
- Two hours after a light breakfast:
  - Measure baseline S_{OSM} and U_{OSM}.
  - Give patient water to drink (20 mL/kg) over 15 to 30 minutes.
- Patient should remain recumbent during test:
  - Collect hourly S_{OSM} and U_{OSM} over the next 4 hours.
  - Measure total urine output over the 4-hour duration.
- Interpretation of results:
  - For all patients, S_{OSM} will acutely drop by greater than 5 mOsm/kg.
  - Normal individuals: Urine WILL be appropriately diluted to U_{OSM} less than 100 mOsm/kg. Ninety percent of water load is typically excreted by 4 hours.
  - Patients with SIADH: Urine WILL NOT appropriately dilute to U_{OSM} less than 100 mOsm/kg, and urine output will be less than 90% of water load.

A1.2 Calculations for Hyponatremia Correction in Patients Receiving Intermittent Hemodialysis (iHD) and Continuous Kidney Replacement Therapy

Correction rates of hyponatremia in the hemodialysis patient:

- Uremic patients are thought to be protected from osmotic demyelinating syndrome (ODS) with overly rapid correction of hyponatremia during dialysis because of the simultaneous removal of uremic solutes.
- However, ODS has been reported in patients with rapid sodium correction with dialysis.
- Correction rates should, therefore, follow the same guidelines for nonuremic patients.
- Calculations of blood flow for iHD: Minimization of sodium correction may be achieved by using the dialysate with the lowest sodium concentration appropriate for patient's *S*[Na^+] level (lowest dialysate [Na^+] is typically 130 mmol/L) and lowest blood flow rate (BFR).
  1. *One can assume that 100% of the [Na^+] difference from the dialysate will transfer to the blood if the blood is allowed to flow very slowly against a high dialysate flow rate of 800 mL/min.*
  2. *Consider a patient with S[Na^+] of 120 mmol/L; goal correction of 6 mmol/L over a 3-hour dialysis session using a dialysate with [Na^+] of 130 mmol/L.*
  3. *Assuming 100% Na^+ transfer from the dialysate, every 1 L of blood that passes through the dialyzer will gain 10 mmol of Na^+.*
  4. *If goal S[Na^+] is 126 mmol/L and the patient has a total body volume of 30 L, the total amount of Na^+ needed is 6 mmol/L × 30 L = 180 mmol. Since every 1 L of blood that passes through the dialyzer picks up 10 mmol of Na^+ from the dialysate, a total blood volume of 18 L (180 mmol/10 mmol/L) would need to pass through the dialyzer over 3 hours. The BFR would thus be 18 L/3 h or 100 mL/min. This may be achieved by using the pediatric mode on the dialyzer.*

  Essentially, to correct hyponatremia with iHD using a dialysate flow of 800 mL/min, the BFR (mL/min) may be estimated as follows:

$$\text{BFR (mL/min)} = \frac{(\text{Total body volume [L]}) \times (\Delta S[Na^+]) \times 1000\ (\text{mL})}{(\text{Dialysate } [Na^+] - S[Na^+]) \times \text{Duration of dialysis treatment (min)}}$$

*where Δ*S*[Na^+] = goal S[Na^+] at end of dialysis − presenting S[Na^+].*
If slow correction rate is limited by the lowest blood flow possible with iHD, consider lowering dialysate flow or switch to continuous kidney replacement therapy.

Calculations for the correction of dysnatremias in patients receiving CKRT

Hyponatremia

- 5% dextrose water (D5W) can be used as postfilter replacement fluid (RF) or separate systemic infusion to slowly correct patients who have hyponatremia:
- D5W rate = [(140 − target Na)/140] × desired clearance.
- For example, using post-dilution continuous venovenous hemodiafiltration (CVVHDF) in a patient with an initial sodium of 120 mmol/L and a target sodium concentration of 130 mmol/L at a desired clearance of 3 L/h using RF or dialysate with 140 mEq/L of sodium, the D5W infusion rate would be [(140 − 130)]/140] × 3 L = 0.214 L/h. The postfilter RF would be 210 mL/h, and the dialysate/prefilter RF would be 3,000 − 214 = 2,786 to 2,790 mL/h.

Hypernatremia

- In patients with cerebral edema who need 3% saline to maintain serum Na concentration in the range of 150 to 155 mmol/L, 3% saline can be delivered as postfilter RF.
- 3% infusion rate = [(target Na − 140)/(513 − 140)] × desired clearance.
- For example, in a patient with an initial sodium of 140 mmol/L and a target sodium concentration of 155 mmol/L at a desired clearance of 3 L/h, the 3% saline infusion rate would be [(155 − 140)/(513 − 140)] × 3 = 0.120 L/h or 120 mL/h. The dialysate/prefilter RF would be 3,000 − 120 = 2,880 mL/h.

Table A1.3 Diuresis and ultrafiltration in patients with acute decompensated heart failure: Summary of major trials

Trials	Aims	*N*	Findings

DOSE	Evaluate efficacy and adverse effects of various loop diuretic strategies:
	• Low dose (1 × outpatient oral dose) vs high dose (2.5 × outpatient oral dose)
	• Bolus q12h vs continuous infusion × 72 h
		308	• There was no statistically significant difference in global symptom relief or change in renal function at 72 h for either:
			  • q12h dosing or continuous infusion
			  • Low dose or high dose
			• High intensification (2.5× oral dose) was associated with trends toward greater improvement in symptom

Trials	Aims	*N*	Findings
			relief (global assessment and dyspnea), weight loss and net volume loss, proportion free from signs of congestion, and reduction in NT-proBNP.
EVEREST	Evaluate the effects of tolvaptan 30 mg daily vs placebo	4,133	• Early benefit in dyspnea on day 1 and edema/weight on day 7, but no benefit on HF hospitalization or mortality

UNLOAD	Evaluate the effectiveness of UF vs aggressive loop diuretic
	• UF arm: UF up to 500 mL/h
	• Diuretic arm: IV diuretics at ≥2 times outpatient oral dose within 48 h of randomization
		200	• Early UF:
			  • Produces greater weight and fluid loss than IV diuretics, without adverse impact on kidney function
			  • Reduces 90-d percentage of patients requiring rehospitalization for HF, number of HF rehospitalizations, days of rehospitalization for HF, emergency department and unscheduled office visits
			• UNLOAD suggested the superiority of UF over diuretics in patients hospitalized for volume-overloaded HF.

CARRESS-HF	Compare the effect of UF with that of stepped pharmacologic therapy on renal function and weight loss in patients with HF who have worsening renal function and persistent congestion following stepped pharmacologic therapy vs UF	188	• The use of a stepped pharmacologic therapy algorithm was superior to a strategy of UF for the preservation of renal function at 96 h. • Similar amount of weight loss was achieved with two approaches. • UF was associated with a higher rate of adverse events. • A substudy of CARRESS-HF suggested that renal function recovery at 60 d was superior in patients with increased tubular injury markers during intensive volume removal by either modality, suggesting the benefits of decongestion may outweigh any modest or transient increases in SCr or tubular injury markers. Note: Compared to UNLOAD trial, the medical arm in the current study using

Trials	Aims	*N*	Findings
			the stepped pharmacologic therapy achieved greater fluid removal. This may have made the difference in outcome.

Abbreviations: CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE, Diuretic Optimization Strategies Evaluation trial; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal proB-type natriuretic peptide; SCr, serum creatinine; UF, ultrafiltration; UNLOAD, Ultrafiltration vs intravenous diuretics for Patients Hospitalized for ADHF.

A1.4 The Use of Vasoconstrictors in Patients With Hepatorenal Syndrome

Terlipressin + albumin

- Terlipressin is a synthetic analog of vasopressin-1a receptor agonist. It raises peripheral vascular resistance, hence blood pressure (BP), and decreases portal venous blood flow and hepatic venous pressure gradient. Its use is contraindicated in patients with ischemic cardiovascular disease (CVD).
- U.S. box warning: Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with acute-on-chronic liver failure grade 3 are at increased risk. Assess oxygenation saturation prior to initiating terlipressin.
- Dosing:
  - Terlipressin 1 to 2 mg intravenous bolus every 4 to 6 hours. Treatment is maintained until serum creatinine (SCr) has decreased to less than 1.5 mg/dL.
  - Albumin 1 g/kg/d up to 100 g/d on day 1, followed by 20 to 40 g/d; may increase to 40 g daily if central venous pressure (CVP) is less than 12 mm Hg (or plasma renin activity [PRA] not reduced by >50% of basal value after 3 days of treatment); monitor serum albumin levels as levels greater than 3 to 4 g/dL likely do not provide added benefit (authors' opinion).

Norepinephrine (NE) + albumin

- NE 0.5 mg/h, to increase mean arterial blood pressure (MAP) by greater than 10 mm Hg or increase in 4-hour urine output greater than 200 mL.

If goals are not met, increase dose every 4 hours in steps of 0.5 mg/h, up to a maximum dose of 3 mg/h.

- Albumin dosing as above

Vasopressin + albumin

- *Vasopressin 0.01 U/min, increase dose to a maximum of 0.8 U/min to achieve increase in MAP ≥10 mm Hg*
- *Albumin dosing as above*
- *Monitor for hyponatremia*

Combination midodrine (systemic vasoconstriction) + octreotide (splanchnic vasoconstrictor) + albumin

- Prior to the FDA approval of terlipressin, the lower efficacy combination of midodrine + octreotide + albumin was widely used in the United States. Octreotide is a synthetic analog of the pancreatic hormone somatostatin, which serves as a splanchnic vasoconstrictor by inhibiting glucagon, a splanchnic vasodilator.
- Midodrine (systemic vasoconstrictor): Start at 7.5 mg orally tid, titrate up to 12.5 to 15 mg tid to increase MAP by at least 15 mm Hg PLUS
- Octreotide (splanchnic vasoconstrictor): Start at 100 µg tid subcutaneously then, if necessary, increase to 200 µg tid PLUS
- Albumin dosing as above

A1.5 Model of End-Stage Liver Disease (MELD) Sodium Score

- MELD sodium is a scoring system used by the United Network for Organ Sharing (UNOS) to prioritize allocation of deceased donor livers for transplantation.
- Factors used in calculating MELD sodium include serum levels of sodium, albumin, bilirubin, and creatinine; international normalized ratio (INR); and patient's sex.
- Scores range from 6 to 40. An increasing score is associated with increasing severity of hepatic dysfunction and 3-month mortality risk in individuals older than 12 years.

- Patients with chronic liver conditions that can reduce survival independent of MELD score can receive adjustments in their MELD score. Standard MELD exceptions include hepatocellular carcinoma, hepatopulmonary syndrome, portopulmonary hypertension (HTN), familial amyloid polyneuropathy, primary hyperoxaluria, cystic fibrosis, hilar/perihilar cholangiocarcinoma, and hepatic artery thrombosis.

UNOS MELD equation

- Original MELD Risk Score equation

$$\text{MELD} = 10 \times ([0.957 \times \ln(\text{SCr})] + [0.378 \times \ln(\text{Bilirubin})] + [1.12 \times \ln(\text{INR})]) + 6.43$$

- If a patient is on hemodialysis, SCr is set to 4, the maximum creatinine level allowed in the model. MELD score can range from 6 to 40 (anything >40 is grouped into 40 maximum), where a higher range indicates higher urgency for liver transplantation (higher mortality risk).

MELD-Na equation (modified from MELD score above)

$$\text{MELD-Na} = \text{MELD} - \text{Na} - (0.025 \times \text{MELD} \times [140 - \text{Na}]) + 140$$

A1.6 Mechanisms of Thiazide-Induced Hyponatremia

- Loop diuretics inhibit Na^+-K^+-$2Cl^-$ cotransporter, hence:
  - **Reduction of medullary concentration gradient.** Optimal H_2O reabsorption at the collecting tubules depends on a high medullary concentration gradient (high medullary tonicity). The lack of a high medullary concentration gradient reduces the efficiency of free H_2O reabsorption.
  - **Reduction in free H_2O production** and consequently, less free H_2O delivery to collecting tubules for reabsorption
  - The impaired free H_2O reabsorption with loop diuretics from mechanisms above "protects" patients from developing hyponatremia despite having increased antidiuretic hormone (ADH).
- Thiazide diuretics do not interfere with the generation of the medullary concentration gradient or reduce luminal free H_2O production as much as loop diuretics. A compensatory increase in ADH with thiazides,

therefore, will still lead to avid free H_2O reabsorption in the presence of any free H_2O intake. Consequently, hyponatremia may develop within 5 to 14 days. At-risk patients include underweight and older women and concurrent low solute intake.

CHAPTER 2: ACID-BASE AND POTASSIUM DISORDERS

A2.1 Proposed Mechanisms for Bicarbonate Generation From the Combined Use of Polystyrene Sulfonate (Kayexalate) and Either Aluminum or Magnesium Hydroxide or Calcium Carbonate

The use of X-OH salt or calcium carbonate in the presence of resin X:

$$X(OH)_2 + \text{Na-resin} + 2HCl \rightarrow XCl_2 + 2\text{Na-resin} + 2H_2O \text{ (stomach)}$$

$$\rightarrow 2NaHCO_3 \text{ (duodenum)} + \text{X-(resin)}_2 + 2NaCl + 2NaHCO_3$$

The use of X-OH salt or calcium carbonate in the absence of resin X:

$$X(OH)_2 + 2HCl \text{ (stomach)} \rightarrow XCl_2 + 2H_2O \text{ (stomach)}$$

$$2NaHCO_3 \text{ (duodenum) } XCl_2 + 2H_2O \rightarrow XCO_3 + 2NaCl + H_2O + CO_2$$

- Similar reactions with newer resins are not yet known. However, patiromer may be expected to be at higher risk than sodium zirconium cyclosilicate as the former has nonspecific cation binding while the latter has selectivity for potassium.

Dad T, Garimella PS, Strom JA. An unusual case of metabolic alkalosis in a patient with CKD. *Am J Kidney Dis.* 2017;69(1):xiii-xvi.

A2.2 Pendrin

- Pendrin is also involved in the electroneutral reabsorption of NaCl in β-intercalated cell (β-IC) by acting in concert with the sodium-driven Cl^--$2HCO_3^-$ exchanger (NDCBE). The NaCl cotransporter NCC in distal convoluted tubules complimentarily acts with β-IC cells in collecting tubules to reabsorb NaCl. Reduced NCC function (eg, mutations or use of NCC inhibitors) will result in compensatory increased Na^+

reabsorption by β-IC and vice versa. Inhibition of both NCC and pendrin can result in severe hypovolemia, metabolic alkalosis, and hypokalemia (**Figure A2.1**).

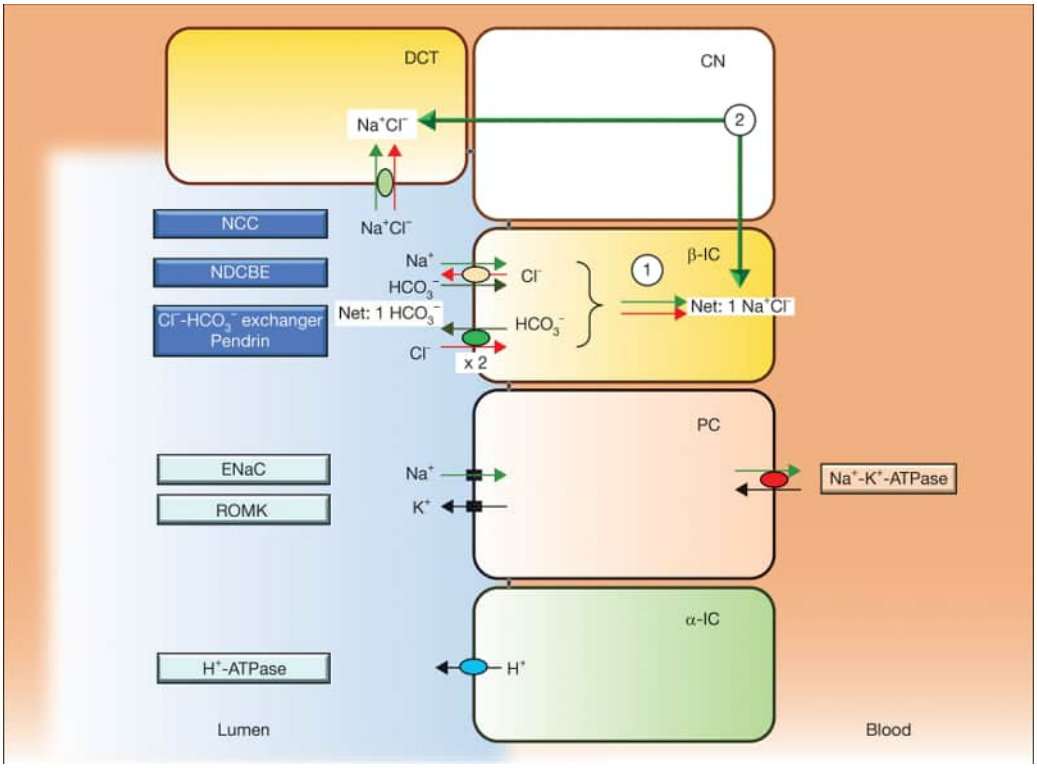


FIGURE A2.1 Complementary electroneutral sodium chloride reabsorption by NCC and NDCBE. 1. In β-IC, pendrin is involved in both HCO_3^- secretion and the electroneutral reabsorption of NaCl by acting in concert with the sodium-driven Cl^--$2HCO_3^-$ exchanger (known as NDCBE). Two cycles of Cl^--HCO_3^- exchange by pendrin and one cycle of $Na^-/Cl^-/HCO_3^-$ exchange by NDCBE lead to a net of 1 HCO_3^- secretion and 1 NaCl electroneutral reabsorption. 2. The NaCl cotransporter NCC in the distal convoluted tubule complementarily acts with the pendrin/NDCBE duo in β-IC cells in the collecting duct to reabsorb NaCl. That is, reduced function of NCC (eg, mutations or use of NCC inhibitors) will result in compensatory increased Na^+ reabsorption by β-IC and vice versa. Inhibition of both NCC and pendrin leads to exaggerated and reduced distal Na^+ reabsorption, increased Na^+ delivery to ENaC, and subsequent increased K^+ and H^+ secretion, all leading to severe hypovolemia, metabolic alkalosis, and hypokalemia.
Abbreviations: α-IC, α-intercalated cell; β-IC, β-intercalated cell; CN, connecting segment between distal convoluted tubule and collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NCC, sodium chloride cotransporter; NDCBE, sodium driven chloride bicarbonate exchanger; PC, principal cell; ROMK, renal outer medullary potassium channel.

- Clinical significance:

- The use of thiazide diuretics in patients with Pendred syndrome can precipitate severe hypovolemia, metabolic alkalosis, and hypokalemia.
- Pendrin expression has been shown to be downregulated by acetazolamide. Combined use of thiazides and acetazolamide may synergistically induce significant diuresis.

A2.3 Apparent 1:1 H^+-K^+ Exchange in Skeletal Muscle Cells in Response to Extracellular pH Changes

Cellular shifts of K^+ in response to plasma pH do not occur via a direct 1:1 exchanger, but via a complex system of transporters that work in concert to achieve the end result of an apparent 1:1 exchange. Mechanisms are illustrated in **Figure A2.2**.

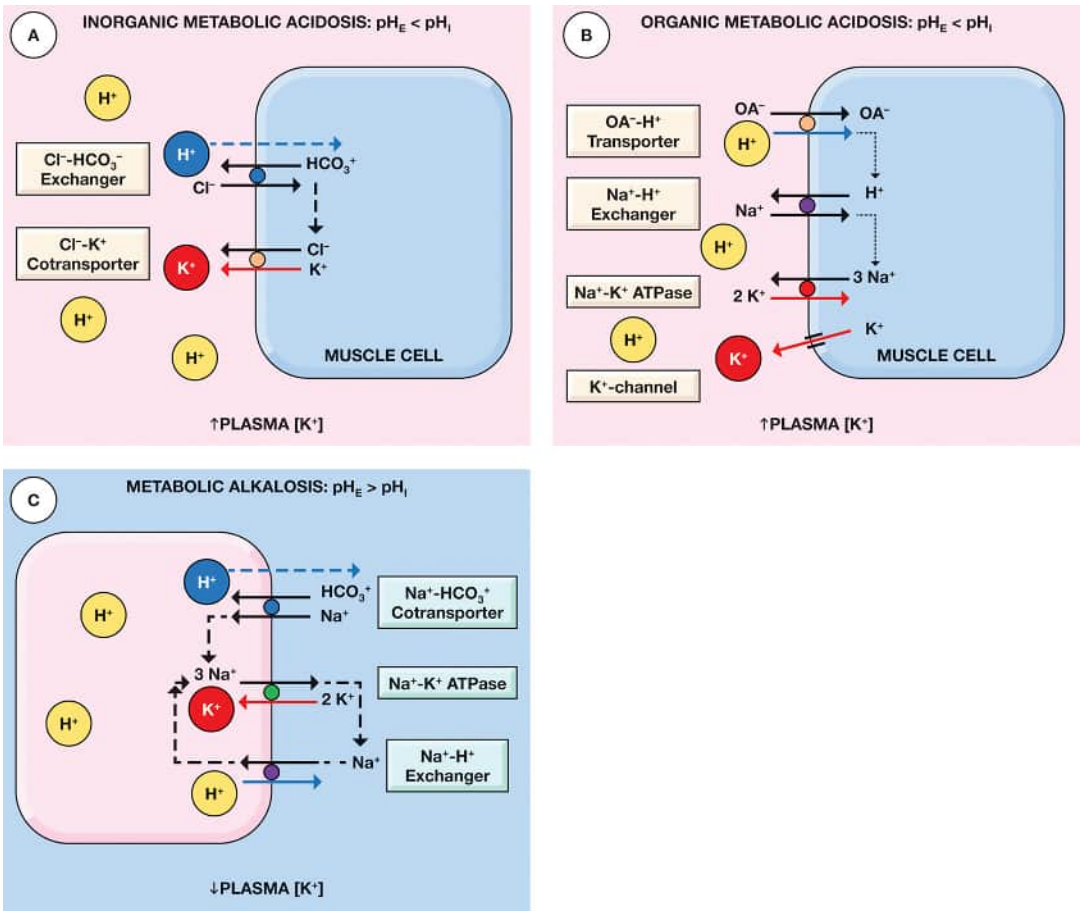


FIGURE A2.2 Changes in extracellular pH (H+ concentration) can lead to increased activities of various transporters, all acting in concert to shift K+ in the opposite direction of favorable H+ movement, thereby giving rise to an "apparent direct K+-H+ exchange." A. H^+/K^+ exchange for inorganic acids. B. H^+/K^+ exchange for organic acid.

The transport of organic acids into the cell increases the Na^+-H^+ exchanger activity and subsequent Na^+-K^+ ATPase. The cellular uptake of K^+ reduces net extracellular K^+ shift compared to that observed with inorganic acid. This explains milder hyperkalemia associated with metabolic acidosis associated with organic acids.

Dashed blue arrow line: The neutralization of H^+ by HCO_3^- gives rise to the apparent movement of H^+ across cell membrane.

Abbreviations: OA^-, organic acid; pH_E, extracellular pH; pH_I, intracellular pH.

CHAPTER 3: CALCIUM, PHOSPHORUS, AND MAGNESIUM DISORDERS AND STONES

A3.1 Mechanism of Action of Lumasiran

Lumasiran (Oxlumo) reduces levels of glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger RNA (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production. As the GO enzyme is upstream of the deficient alanine: glyoxylate aminotransferase (AGT) enzyme that causes primary hyperoxaluria type 1 (PH1), the mechanism of action of lumasiran is independent of the underlying AGXT gene mutation. OXLUMO is not expected to be effective in primary hyperoxaluria type 2 (PH2) or type 3 (PH3) because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2 and PH3. Whether the advent of lumasiran obviates the need for liver transplantation is an area of intense clinical research.

CHAPTER 4: CHRONIC KIDNEY DISEASE

A4.1 Equations Used to Estimate Glomerular Filtration Rate (eGFR) Other Than CKD Epidemiology Collaboration (CKD-EPI)

Modification of Diet in Renal Disease (MDRD) study

- Derived from patients with CKD
- MDRD equations were derived based on urinary clearance of ^{125}I-iothalamate.

MDRD-4 variables (age, gender, race [African American vs non–African American], calibrated standardized SCr). SCr should be measured by

specific assay traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.

MDRD-6 variables (age, gender, race [African American vs non–African American], calibrated standardized SCr, albumin, blood urea nitrogen [BUN])

Limitations of MDRD equations

- *Underestimate* GFR in patients with GFR greater than 60 mL/min/1.73 m^2, which overreports the incidence of CKD. Many laboratories report eGFR greater than 60 as "greater than 60 mL/min/1.73 m^2" rather than an actual calculated value due to inaccurate estimates in patients with higher GFR range.
- Not validated in geriatric patients, children, and pregnant women
- Not validated in non–steady states such as acute kidney injury (AKI)
- Not derived for races other than "White" or "African American"
- Both MDRD-4 and Cockcroft-Gault equations overestimate true GFR in sick hospitalized patients.
- Incorporation of BUN and albumin (MDRD-6) partially improves GFR estimates at the expense of increasing complexity.

Advantages of CKD-EPI over MDRD

- Similar accuracy as MDRD for GFR less than 60 mL/min/1.73 m^2
- Better accuracy for eGFR greater than 60 mL/min/1.73 m^2
- Lower CKD prevalence (since CKD-EPI[SCr] is better at estimating higher GFR)
- Better accuracy for risk predictions
- Applicable across more diverse population

Advantages of MDRD over CKD-EPI:

MDRD performs better and provides better accuracy in estimating GFR in individuals with severe obesity.

A4.2 Factors Contributing to CKD Progression

Angiotensin II

- Increases plasma protein filtration via both hemodynamic effect and direct podocyte effect, the latter via stimulation of AT_1R
- Increases oxidative stress–associated injury, synthesis of cytokines, chemokines, tumor growth factor-β (TGF-β), connective tissue growth factor, chemotactic and cell adhesion molecules, all leading to increased plasma mesangial cell proliferation, extracellular matrix synthesis, and macrophage activation and infiltration.
- Increases aldosterone synthesis. Aldosterone increases plasminogen activator–*inhibiting* factor I (PAI-I). Plasminogen activator normally induces proteolysis. Plasminogen activator *inhibitor* PAI-I reduces mesangiolysis and fibrinolysis, thus favoring mesangial expansion and fibrosis.

Proteinuria

- Proteinuria comprising of nonspecific pro-inflammatory proteins can lead to direct tubular injury and/or complement activation with resultant tubulointerstitial inflammation.
- Exposure of tubular epithelial cells to a high-protein concentration can increase the synthesis of endothelin 1, a potent vasoconstrictor and a stimulator of renal cell proliferation and extracellular matrix and TGF-β synthesis. TGF-β is known to increase collagen and fibronectin production, which play a key role in tissue fibrosis.
- Higher degree of albuminuria is associated with an increased risk of end-stage kidney disease (ESKD).

A4.3 U.S. Policies in the Care of Patients With ESKD

U.S. prospective payment system for ESKD

- In 2011, the US Centers for Medicare and Medicaid Services launched the prospective payment system (PPS) for ESKD care, when the "bundled" payment system was created.
- This policy:
  - Limits the use of some medications and services in patients with ESKD
  - Increases monthly margin payment per PD compared with HD patient. Prior to this policy, payments favored adding an HD over PD patient.

- The Study to Evaluate the Prospective Payment System Impact on Small Dialysis Organizations (STEPPS) revealed:
  - A decline in erythropoietin-stimulating agent (ESA) doses and mean hemoglobin (Hb) levels which coincided with the transition to PPS.
  - African American patients who tend to have higher ESA requirements to achieve target Hb were noted to have greater reductions in ESA doses in association with a greater proportion of patients with Hb less than 10 g/dL, and greater need for transfusions, compared to other groups. Long-term patient outcomes of PPS are needed.
  - Decrease in intravenous vitamin D analogs and an increase in oral therapies
  - Increase in serum parathyroid levels from 273 to 324 pg/dL (acceptable parathyroid hormone [PTH] level 150 to 9 times the normal levels or 600 pg/dL)

Advancing American Kidney Care

- In July 2019, the Centers for Medicare & Medicaid Services's (CMS) Advancing American Kidney Care aimed to improve chronic kidney disease (CKD) and ESKD outcomes. The proposed initiatives are as follows:
  - The CMS initiated mandatory participation by 50% of dialysis units to enter the End-stage Renal Disease Treatment Choices (ETC) model in 2020, which encourages greater use of home dialysis and kidney transplants for Medicare beneficiaries with ESKD, while reducing Medicare expenditures.
  - Four voluntary kidney models include the Kidney Care First (KCF) and Comprehensive Kidney Care Contracting (CKCC) graduated, professional, and global models.
  - KCF, available to participating nephrologists and nephrology practices, will receive adjusted fixed capitated payments for managing care of aligned beneficiaries with CKD stage 4 or 5 and those on dialysis. A bonus payment will be added for every patient who receives a kidney transplant (if functional up to 3 years).
  - CKCC model, available to nephrologists, transplant providers, and dialysis facilities, will take responsibility for the total cost and quality

of care for the patient, and in exchange, can receive a portion of the Medicare savings they achieve.

- CKCC graduated model, based on the existing Comprehensive ESKD Care (CEC) model one-sided risk, begins under a lower reward one-sided model and incrementally phase in to greater risk and greater potential reward.
- CKCC professional, based on the Professional Population-Based Payment option of the direct contracting model, allows opportunities to earn 50% of shared savings or be liable for 50% of shared losses based on the total cost of care for Part A and B services.
- CKCC global model, based on the Global Population-Based Payment option of the direct contracting model, allows provides to risk 100% of the total cost of care for all Parts A and B services for aligned beneficiaries.
- By 2025, 80% of new ESKD starts will be receiving home dialysis or kidney transplant was outlined in an executive order.

Self-referral and Stark law

- Started in 1989 barring medical directors to self-refer patients to own unit where there is a "financial relationship." It was later recognized that Stark law would prevent medical directors from practicing patient care.
- Later amendments exempted medical directors to refer patients to own dialysis units.

A4.4 Common Terms Used in Dialysis

Ultrafiltration coefficient, KUF: Characteristic of membrane, expressed as mL/h/mm Hg of transmembrane pressure (TMP) applied

$$\text{TMP} = \text{Desired UF}/K_{UF}$$

Example: K_{UF} of 10 mL/h/mm Hg implies that in order to ultrafiltrate 500 mL/h, a TMP of 50 mm Hg would have to be applied.

Dialyzer clearance, KoA

- KoA is the maximum theoretical clearance of any dialyzer. True solute removal is typically 5% to 30% less than published KoA.

- Choosing a dialysis KoA for a patient depends on blood flow, dialysate flow, and desired urea clearance to meet a specified K_t/V.

Standardized K_t/V (Std K_t/V) is a continuous clearance equivalent that takes into account the continuing generation of the solute being cleared. Std K_t/V may be used to compare any form of dialysis (home, daily, conventional, peritoneal dialyses).

Membrane efficiency versus flux

- Efficiency implies the amount of solute removed. High efficiency may be obtained with large surface area membranes. A high-efficiency dialysis membrane may have either small or large pores and can remove small and/or large molecules.
- High flux implies the ability to remove larger molecules such as β2-microglobulins. High-flux dialyzer membranes have larger pores.

A4.5 K_t/V

- *Kt*/*V* of a solute is the *proportion of volume V that has undergone clearance of that specific solute over duration of time t*, where
  - *K* represents the clearance capacity,
  - *t* = the duration over which the clearance process takes place, and
  - *V* = the entire volume that is subjected to the clearance process.
- Interpretations of K_t/V for solute A:
  - *K_t/V = 1 means that the total volume *V* has been completely cleared of solute A over time *t*.
  - *K_t/V = 0.6 means that 60% of *V* has been cleared of solute A. *Assuming no mixing of cleaned volume with "dirty" volume.
  - If there is mixing of cleaned volume back into the "dirty" volume, a K_t/V of 1 does not necessarily mean that all of solutes A have been cleared out. Clinically, when 250 mL of blood from a patient has been dialyzed, it is returned back into circulation, "mixed" with nondialyzed blood, then undergoes further dialysis. The remixing process does not allow for complete clearance of urea despite having passed an amount of blood equivalent to the patient's total body volume through the dialyzer. This explains why a patient with a urea K_t/V of

1.5 or 2.0, etc, which technically means that 1.5 or 2.0 times the patient's total body volume *V* have gone through the dialyzer, still does not achieve a BUN level of 0 mg/dL.

- Currently, creatinine and urea clearances are commonly used as surrogates for all other (toxic) metabolite clearance.

A4.6 Techniques That May Be Used to Help Optimize Ultrafiltration (UF)

- Point-of-care ultrasound to measure B line as a marker of lung water
- Blood volume monitoring (BVM, also known as "crit-line"): a method whereby blood volume (plasma volume) changes are detected by changes in intravascular hematocrit (Hct). Theoretically, when the UF rate is the same as the rate of interstitial fluid mobilizing into the intravascular volume, there is no change in Hct. When the UF rate is higher than that of interstitial fluid moving into the intravascular space, Hct is expected to increase. BVM is designed to reduce hypotension episodes during UF with HD, but it does not directly detect the excess volume in interstitial space and cannot determine dry weights in HD patients.
- Bioimpedance: a method whereby current frequencies ranging from 5 to 1,000 kHz are passed through the skin. While low-frequency currents preferentially pass through the extracellular fluid space due to its inability to penetrate cell membranes, high-frequency current can penetrate the extracellular and intracellular space. Comparisons of these values to those of nonuremic patients can help quantify total body water volume, intracellular and extracellular volumes in dialysis patients.

A4.7 Conventional Indices for Urea Clearance

Urea reduction ratio (URR)

- URR = (pre − post)/pre = (1 − post/pre), which may also be expressed as %
- Example: predialysis BUN 100 mg/dL, postdialysis BUN 66 mg/dL
- URR = (100 − 66)/100 = 0.34% or 34%

Single pool K_t/V (spK_t/V) of urea

- This is a dimensionless ratio, which represents the fractional clearance of urea from a single pool, where
  - K = dialyzer blood water urea clearance (L/h)
  - t = dialysis duration (h)
  - V = volume of distribution of urea (L). Since we cannot "drain" the entire patient's body volume *V* to pass through the dialyzer at any single time point, the volume that passes through the dialyzer is from a continuous mixture of dialyzed and nondialyzed volumes. Clearance of any solute thus follows a natural logarithmic (decay) pattern, hence

$$\text{sp}K_t/V = -\ln(1 - \text{URR})$$

- What would URR be when $\text{sp}K_t/V = 1$ (ie, the whole tank volume has gone through dialysis)?
  - $1 = -\ln(1 - \text{URR})$, solving for URR:

With the continuous remixing of dialyzed to nondialyzed volumes, the *maximum portion of the total body volume V* that is completely cleared of urea after running the entire body volume sequentially through the dialyzer is 0.63.

- Note the $\text{sp}K_t/V$ equation above does not take other factors into account:
  - Continuing urea generation (while dialysis is going on)
  - UF alters the volume *V*, thus K_t/V.
  - With corrections for the above factors, $\text{sp}K_t/V$ becomes
  - $\text{sp}K_t/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55 \times \text{UF}/V$, where
    - $0.008 \times t$ takes into account the continuing urea generation, and
    - $(4 - 3.5 \times R) \times 0.55 \times \text{UF}/V$ takes into account UF, and
    - $R = 1 - \text{URR}$

Inbound versus rebound (multipool model)

- A solute such as urea is sequestered into other compartments (not just single pool).
- Inbound refers to the sequestration/movement of urea (solutes) into other compartments during dialysis.

- Rebound refers to the release of urea (solutes) from other compartments into the blood volume that is accessible to dialysis.
- These occurrences lead to the concept of equilibrated K_t/V (eK_t/V). This is measured 30 to 60 minutes postdialysis.
- In general, $eK_t/V = spK_t/V$ – rebound. To measure rebound, blood sampling is measured 30 to 60 minutes postdialysis. To avoid waiting, eK_t/V may be estimated to be ~0.8 × K_t/V (ie, eK_t/V is typically 20% less than K_t/V).
- What is the difference between whole blood versus plasma clearance? Solute clearance per 1 L of whole blood is lower than that for 1 L of plasma volume. Whereas solutes dissolved in plasma are accessible to dialysis, solutes inside red blood cells are not accessible to dialysis.
- How does increasing Hb level affect dialysis clearance? Correction of anemia does lead to reduced solute clearance. More dialysis may be needed to achieve the same goal K_t/V.

A4.8 Peritoneal Equilibrium Testing Protocol

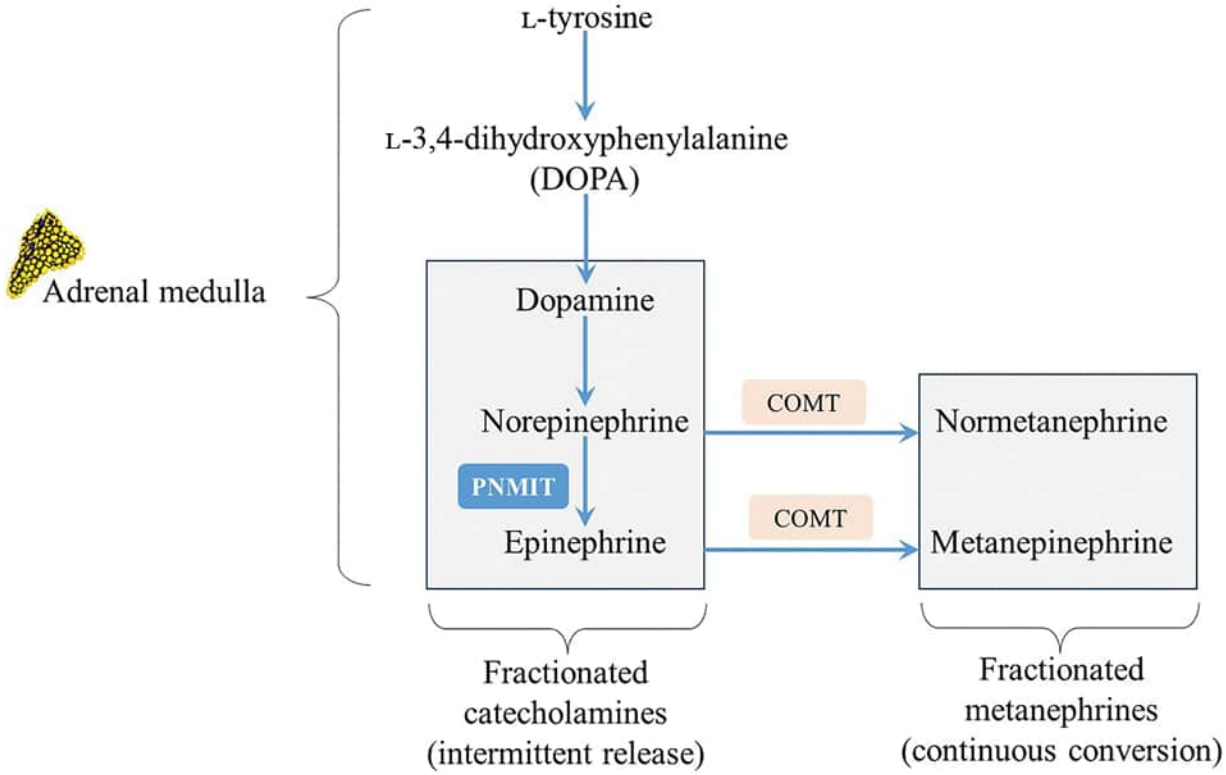
1. Drain peritoneal cavity, ideally after an 8 to 12 hours overnight dwell using 2 L of 2.5% dextrose dialysate.
2. Weigh a 2 L bag of warmed 2.5% dextrose dialysate.
3. Infuse bag and have patient roll from side to side after each 400 mL of dialysate.
4. Blood and dialysate samples are taken at 4 hours for urea, creatinine, glucose, and sodium for calculations of dialysate/plasma concentration ratios of respective solutes (D/P) to determine the patient's transporter type. For glucose, calculation of the ratio D/D_0 is used to determine the patient's transporter type, where D is the dialysate glucose at 4 hours of dwell, and D_0 is the dialysate glucose at the start of dwell.
5. At 4 hours, dialysate is drained and the whole bag reweighed. Difference in weight is UF volume.

CHAPTER 5: HYPERTENSION

A5.1 Data Regarding Medical Versus Invasive Therapy for Renal Artery Stenosis

- Cardiovascular Outcomes of Renal Atherosclerotic lesions (CORAL) trial: comparative trial for renal artery stenting versus best medical therapy involving 947 patients with uncontrolled HTN and atherosclerotic renal artery stenosis, BP greater than 155 mm Hg while on more than two antihypertensive drugs
  - Average systolic BP (SBP) was 2.3 mm Hg lower in the stent group throughout the trial (median follow-up 3.6 years).
  - No difference in incidence of CV or renal death, myocardial infarction (MI), hospitalization for congestive heart failure (HF), stroke, progressive CKD, or need for renal replacement therapy
- Meta-analysis of five randomized controlled trials (RCTs) involving 1,159 patients comparing percutaneous renal artery revascularization (with or without stenting) versus medical therapy on the future occurrence of nonfatal MI: Renal revascularization did not affect the risk of nonfatal MI.

A5.2 Synthesis of Catecholamines



- The rate-limiting step in the synthesis of catecholamine occurs at the initial conversion of L-tyrosine into L-3,4-dihydroxyphenylalanine (DOPA) via the enzyme tyrosine hydroxylase. DOPA is subsequently converted to dopamine. Dopamine is hydroxylated into L-NE, which is then converted into epinephrine. The conversion of NE to epinephrine requires the cortisol-induced enzyme, phenylethanolamine-*N*-methyltransferase (PNMT).
- NE and epinephrine are converted into their metabolites, normetanephrine and metanephrine, respectively, by the enzyme catechol-*O*-methyltransferase (**COMT**).
- Catecholamines (NE, epinephrine) are released intermittently, while the intratumoral conversion of catecholamines into their metabolites (normetanephrine, metanephrine) occurs continuously. This is why screening with fractionated metanephrines is more sensitive than fractionated catecholamines. Screening with fractionated catecholamines may miss pheochromocytoma/paraglioma (PPGL) because catecholamines are intermittently released.
- Fractionated catecholamines include dopamine, NE, and epinephrine.
- Fractionated metanephrines include the metabolites of epinephrine and NE, which are metanephrine and normetanephrine, respectively.
- Cortisol stimulates **PNMT**. Significant elevation of epinephrine or metanephrine (metabolite of epinephrine) generally implies the presence of adrenal PNMT, a cortisol-induced enzyme. Although PNMT is present in extra-adrenal tissues (paraganglia), it is not under paracrine stimulation by cortisol and, therefore, does not convert NE into epinephrine.

MyEndoConsult. Accessed July 16, 2024. https://myendoconsult.com/learn/what-are-plasma-metanephrines

A5.3 Familial Hyperaldosteronism

Familial hyperaldosteronism type II

Germline heterozygous gain-of-function mutation in the voltage-gated chloride channel ClC-2. The associated increased chloride conductance at resting potentials results in increased expression of aldosterone synthase and aldosterone secretion.

Familial hyperaldosteronism type III

Somatic mutation in the gene encoding the potassium channel KCNJ5 in one-third of adenomas (mutation in affected tissues only): Potassium selectivity of the channel is lost, thus allowing sodium influx through the channel and subsequent chronic cell depolarization. This leads to calcium influx and consequent activation of aldosterone synthase and cell proliferation.

Familial hyperaldosteronism type IV

Somatic mutation in the gene encoding the voltage-gated calcium channel CACNA1D can lead to increased calcium influx and subsequent activation of aldosterone synthase and cell proliferation.

A5.4 Clinical Data Regarding Thiazide Diuretics and CV Outcomes

- 2015 meta-analysis involving 14 RCTs comparing hydrochlorothiazide (HCTZ) versus chlorthalidone (CTDN) and indapamide (INDAP):
  - CTDN and INDAP reduced SBP by −3.6 and −5.1 mm Hg more than HCTZ, respectively.
  - No differences in metabolic adverse effects were detected.
- 2.5 mg INDAP reduced stroke by 29% and all CV events by 23% in the Post Stroke Antihypertensive Treatment Study. Perindopril-INDAP combination also reduced CV events in two other placebo-controlled trials.
- In an observational cohort study, CTDN was associated with lower left ventricular hypertrophy (LVH) compared to HCTZ. In another observational cohort analysis (n = 12,866), the percentage risk reduction in CV events from CTDN versus HCTZ was 21%. In network meta-analyses of randomized trials (n = 50,946), CTDN conferred a 25% risk reduction in congestive HF and CV events compared with HCTZ.
- 2022 Veterans Affairs trial of thiazide diuretics at doses commonly used in clinical practice: At median follow-up of 2.4 years, patients with a mean age of 72 years who received CTDN did not have a lower occurrence of major CV outcome events or non–cancer-related deaths

compared with those who received HCTZ. Hypokalemia was notably more common with CTDN compared with HCTZ.

A5.5 Clinical Data Regarding the Use of Spironolactone in Difficult-to-Treat HTN

Anglo-Scandinavian Cardiac Outcomes trial revealed that the addition of spironolactone at a median dose of 25 mg daily in addition to 2.9 other antihypertensive medications lead to a fall in BP of 21.9/9.5 mm Hg at 1.3 year-follow-up. Optimum Treatment of Drug-Resistant Hypertension Study revealed the addition of spironolactone at 25 to 50 mg qd over a 12-week treatment period reduced SBP by 8.7 mm Hg on average compared to placebo.

A5.6 Clinical Data Regarding the Use of Finerenone in Treatment-Resistant HTN

In 624 FIDELITY-TRH patients and 295 AMBER patients

The least squares mean change in SBP from baseline

- −7.1 mm Hg for finerenone
- −1.3 mm Hg for placebo (between-group difference, −5.74 mm Hg, $P <$ .0001)
- −11.7 mm Hg for spironolactone + patiromer
- −10.8 mm Hg for spironolactone + placebo (between-group difference, −1 mm Hg, $P = .58$)

Incidence of serum $[K^+] \geq 5.5$ mmol/L

- 12% for finerenone
- 3% for placebo
- 35% for spironolactone + patiromer
- 64% for spironolactone + placebo

Agarwal R, Pitt B, Palmer BF, et al. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. *Clin Kidney J*. 2023;16(2):293-302.

A5.7 Direct Renin Inhibitor (DRI) Combination With Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB)

Aliskiren in the evaluation of proteinuria in diabetes (AVOID) trial

- Combination therapy consisting of losartan and aliskiren was minimally beneficial compared to lone losartan therapy in patients with type 2 diabetes mellitus (DM) with urine albumin-to-creatinine ratio greater than 300 mg/g.
- Combination therapy was associated with higher rate of hyperkalemia (4.7% vs 17%).

Aliskiren in type 2 diabetes using cardio-renal endpoints (ALTITUDE) trial

- Combination therapy with aliskiren and either an ACEi or ARB in patients with diabetic kidney disease (DKD) reduced SBP by 1 to 2 mm Hg and proteinuria compared with placebo group receiving either ACEi or ARB alone.
- 25% greater stroke rate and more frequent hyperkalemia were observed with combination therapy.

CHAPTER 6: TUBULAR, INTERSTITIAL, AND CYSTIC DISORDERS

A6.1 Future Directions in the Diagnosis of Acute Interstitial Nephritis (AIN)

- Urinary T-cell–derived cytokines (eg, urine interleukin-9 [IL-9], tumor necrosis factor-α [TNF-α])
  - IL-9 is produced from Th9 cells and leads to mast cell accumulation. Of interest, mast cells are seen in kidney biopsies of patients with AIN.
  - Elevated IL-9 may be seen in allergic conditions (eg, dermatitis, asthma, food allergy).
  - The use of corticosteroids in biopsy-proven AIN with associated high urine IL-9 had higher 6-month follow-up eGFRs compared with those with low IL-9 levels.

- Urinary macrophage subtypes: Urine sediment of M1 to M2 macrophages may help differentiate between AIN and other kidney pathologic conditions.
- Urinary retinol-binding protein-to-creatinine ratio (uRBP/Cr): uRBP/Cr ratio was shown to be significantly increased among immune checkpoint inhibitor (AKI vs nonexposed AKI).

A6.2 Mutations Involving Genes Other Than PKD1 and PKD2 That Can Lead to Autosomal Dominant Polycystic Kidney Disease (ADPKD)

***GANAB* gene** encodes the α subunit of glucosidase II. The heterodimeric enzyme glucosidase II plays a role in protein folding and processing of immature glycoproteins in the endoplasmic reticulum (ER). Mutations in this gene are associated with maturation and localization defects of PC1 and PC2, thus ADPKD and autosomal dominant polycystic liver disease (ADPLD) phenotypes. GANAB mutation is thought to account for approximately 0.3% of total ADPKD.

***ALG9* gene** *encodes* an α-1,2-mannosyltransferase enzyme that functions in lipid-linked oligosaccharide assembly. Mutations in this gene result in congenital disorder of glycosylation type Il and impaired polycystin-1 maturation.

***DNAJB*11 gene** encodes a soluble glycoprotein of the ER lumen that functions as a co-chaperone of binding immunoglobulin (Ig) protein, a 70-kDa heat shock protein chaperone required for the proper folding and assembly of proteins in the ER.

Unknown genes: 7% to 10% of all ADPKD cases are genetically unresolved.

A6.3 Total Kidney Volume (TKV) per Height Calculation

TKV/height = sum of (kidney length × width × depth [cm] × π/6) of both kidneys/height (m)

A6.4 Other Potentially Beneficial Medical Therapies

Other potentially beneficial therapies in the treatment of ADPKD but still lacking robust supporting data

Mammalian target of rapamycin (mTOR) inhibitors

- Increased signaling of the mTOR complex is thought to enhance cystic growth in ADPKD. Two clinical studies involving sirolimus, however, have not shown benefits in TKV or kidney function at 18 month-follow-up. Notably, urine albumin-to-creatinine ratio was higher in the sirolimus group (Sirolimus for ADPKD [SUISSE] study).
- Everolimus (mTOR inhibitor): slowed TKV increase but no slowing of eGFR decline detected over a 2-year study period

Somatostatin and somatostatin analogs

Octreotide

- A Long-Acting Somatostatin on Disease Progression in Nephropathy due to ADPKD (ALADIN):
  - Somatostatin analog octreotide-LAR resulted in a trend for smaller TKV increase and better secondary outcome of kidney function (small study).
  - Not yet recommended due to lack of larger trials
- Developing Interventions to Halt Progression of ADPKD 1 (DIPAK 1) trial involving the use of lanreotide
  - Lanreotide reduced the annual increase in TKV (4.1% vs 5.6% per year), but failed to slow GFR decline.
  - The drug was associated with serious adverse events, including hepatic cyst infection.

Somatostatin analogs (lanreotide) and pansomatostatin analogs (pasireotide)

- May reduce kidney and liver cyst fluid accumulation
- Have not been shown to slow GFR decline

HMG-CoA reductase inhibitor (statin): The use of pravastatin in children treated with ACEi revealed slower rates of TKV growth and reduced rate of GFR decline.

Others

- src/bcr-abl tyrosine kinase inhibitor bosutinib (activation of tyrosine kinase receptors for multiple growth factors may activate cystic cell

proliferation), multikinase inhibitor KD019, vitamin K_3, nicotinamide, metformin, pioglitazone, triptolide, dietary interventions

- Calcimimetics have been shown to reduce kidney volume in patients undergoing hemodialysis over long-term follow-up.

CHAPTER 7: GLOMERULAR AND VASCULAR DISORDERS

A7.1 Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV)—Kidney Disease: Improving Global Outcomes (KDIGO 2024)

Prednisolone tapering regimen for AAV

[a]Prednisolone tapering regimen for AAV

Week	<50 kg	50-75 kg	>75 kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5
>52	Investigators' local practice		

In general, oral prednisolone should be reduced to 5 mg/d by 6 months following cyclophosphamide (CYC) induction and withdrawn by 6 months following rituximab (RTX) induction.

[a]Prednisolone tapering regimen for AAV based on reduced-corticosteroid dose in PEXIVAS trial. Initial oral dose is approximately 1 mg/kg/d week 1, half-dose week 2, quarter dose weeks 7 and 8, and 1/10th dose by week 15.

Adapted from Floege J, Jayne DRW, Sanders JSF, Tesar V, Rovin BH. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. *Kidney Int*. 2024;105(S3):S71-S116, with permission from Elsevier.

Induction options for AAV					
[a]RTX	IV CYC	Oral CYC	RTX + CYC	MMF	[b]Avacopan
375 mg/m^2/wk × 4 wk **OR** 1 g at weeks 0 and 2	15 mg/kg at weeks 1, 2, 4, 7, 10, 13 Additional dosing at weeks 16, 19, 21, 24 if required	2 mg/kg/d × 3 mo, continue for a maximum of 6 mo based on ongoing disease activity	RTX 375 mg/m^2/wk × 4 wk plus IV CYC 15 mg/kg at weeks 0 and 2 **OR** RTX 1 g at 0 and 2 wk + IV CYC 500 mg/2 wk × 6	1,000-1,500 mg bid (higher range for poor response)	30 mg bid **in lieu of** GC in combination with RTX or CYC induction
RTX is preferred if • PR3-ANCA • Treating relapse • SCr <4 mg/dL • Fertility concerns • Frail older patients • Steroid sparing is a high priority.	**CYC is preferred if** • RTX not available • SCr ≥4 mg/dL or rapidly declining GFR • Vital organ/life-threatening disease **IV is preferred to oral CYC in:** • Preexisting moderate cumulative CYC dose • Lower WBC • Medical nonadherence • Easy access to an infusion center	**Oral is preferred to IV CYC:** • Cost • No access to infusion center • Adherence is not an issue **Dose reduction:** Age: 70 y$^+$ 1.0 mg/kg/d 60 y$^+$ 1.5 mg/kg/d GFR: <30 mL/min/1.73 m^2 1.5 mg/kg/d	**In patients with SCr ≥3.4 mg/dL or vital organ/life-threatening disease:** Combination of 4 weekly infusions of RTX and 2 IV pulses of CYC can be considered as an alternative to 3-6 mo of CYC. This combination resulted in a similar rate of remission and adverse	May consider in nonsevere disease	• May consider in place of GC in patients with increased risk of GC toxicity, for example, high infection risk, DM, psychiatric disorders, osteoporosis • Patients with lower eGFR may have greater recovery: For whole ADVOCATE study cohort (n=330, 81% with renal involvement),

[a]RTX	IV CYC	Oral CYC	RTX + CYC	MMF	[b]Avacopan
	Dose reduction: Age 70 y^{+} 10 mg/kg 60 y^{+} 12.5 mg/kg GFR <30 mL/min/1.73 m^2 12.5 mg/kg/d		events as CYC in the RITUXVAS trial.		eGFR increased by 7.3 ml/min/1.73 m^2 vs 4.1 ml/min/1.73 m^2 for avacopan vs GC respectively. For eGFR ≤20, eGFR increased by 16.1 vs 7.7 respectively.

Abbreviations: CYC, cyclophosphamide; DM, diabetes mellitus; GC, glucocorticoid; GFR, glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil; RTX, rituximab; SCr, serum creatinine.

[a]KDIGO 2024 recommends that GCs in combination with CYC or RTX be used as the initial treatment of new-onset ANCA-associated vasculitis (1B).

[b]Avacopan may be used in lieu of GCs.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 Clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int.* 2024;105(3S):S71-S116.

Recommendations for dosing and duration[a] of maintenance therapy for AAV

[b]Rituximab	Azathioprine	Mycophenolate mofetil
• For patients induced with RTX, continue RTX for maintenance. • 500 mg × 2 at complete remission, and 500 mg at months 6, 12, and 18 thereafter (MAINRITSAN) OR 1,000 mg IV after induction of remission, and at months 4, 6, 12, and 16 after the first infusion (RITAZAREM)	• For CYC induction, switch to AZA for maintenance. • Dose AZA at 1.5-2 mg/kg/d at complete remission until 1 y after diagnosis then decrease by 25 mg every 3 mo	1,000 mg bid, at complete remission for 2 y
	Extend AZA at complete remission until 4 y after diagnosis; start at 1.5-2 mg/kg/d for 18-24 mo, then decrease to 1	

[b]Rituximab	Azathioprine	Mycophenolate mofetil
	mg/kg/d until 4 y after diagnosis, then taper by 25 mg every 3 mo. GC should also be continued at 5-7.5 mg/d for 2 y and slowly reduced by 1 mg every 2 mo.	
RTX alone may be preferred if: • PR3-ANCA disease Relapse disease Frail older adults • AZA intolerance, for example, patients with thiopurine methyltransferase (TPMT) deficiency—The diagnosis may be made with measuring TPMT activity or genetic testing. • Steroid avoidance is important.	**AZA plus GC may be preferred if:** • Total IgG is <300 mg/dL. • Hepatitis B surface antigen is positive. • RTX availability is limited.	**Other maintenance agents** in nonsevere disease or if RTX and CYC cannot be used: • MMF maintenance is less effective in preventing relapse compared with AZA. • AZA and methotrexate (MTX) have been shown to be equally effective. MTX should not be used in patients with GFR <60 mL/min/1.73 m^2.

[a]Optimal duration of therapy of between 18 months and 4 years after the induction of remission.

[b]RTX can be dosed on a fixed schedule or upon reappearance of $CD19^+$ B cells and/or ANCA, but dosing based on B-cell counts led to fewer infusions and thus lower cost.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 Clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int*. 2024;105(3S):S71-S116.

Plasma exchange (PLEX) dosing and frequency for ANCA-associated vasculitis (KDIGO)		
AAV with severe kidney disease (SCr >3.4 mg/dL), requiring dialysis, or rapidly increasing SCr	**AAV with diffuse pulmonary hemorrhage and hypoxemia**	**AAV in association with anti-glomerular basement membrane (GBM) antibodies**
Seven treatments over a maximum of 14 d, 60 mL/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh frozen plasma	Daily for 14 d or until anti-GBM antibodies are undetectable
Safety precautions Monitor coagulation studies (eg, prothrombin time, activated prothrombin time, and fibrinogen level), immunoglobulin G (IgG), ionized calcium, and potassium levels. Hold ACEi 24-30 h prior to PLEX for possible kinin-derived anaphylactic-like symptoms.		

AAV with severe kidney disease (SCr >3.4 mg/dL), requiring dialysis, or rapidly increasing SCr	AAV with diffuse pulmonary hemorrhage and hypoxemia	AAV in association with anti-glomerular basement membrane (GBM) antibodies
For increased INR, replace with fresh frozen plasma. Initial dose 10-15 mL/kg should increase plasma coagulation factors by ~15%-25%. For fibrinogen level <100-150 mg/dL, replace with cryoprecipitate. One unit of cryoprecipitate typically raises the plasma fibrinogen concentration by ~7-10 mg/dL in a 70-kg patient (10 units raise the fibrinogen concentration by 70-100 mg/dL). For IgG <500 mg/dL or the presence of systemic infection, consider a single infusion of Ig 100-400 mg/kg.		

Adapted from Floege J, Jayne DRW, Sanders JSF, Tesar V, Rovin BH. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. *Kidney Int*. 2024;105(S3):S71-S116, with permission from Elsevier.

A7.2 Pathogenesis of Lupus Nephritis

- Production of autoantibodies by mature B cells (plasma cells) against nuclear antigens (eg, double-stranded DNA [dsDNA]), ribonucleoproteins, complement factors (eg, C1q). This process may be driven by:
  - Antigenic mimicry: antibodies against bacterial or viral peptides cross-react to self-antigens
  - Impaired clearance of apoptotic bodies
  - Polyclonal hyperactivity of the B-cell system or defects of T-cell autoregulation leading to high antibody production. B-cell–activating factor (BAFF), a.k.a. B-lymphocytic stimulator (BlyS), is a cytokine expressed in cells of B-cell lineage that acts as a potent B-cell activator.
  - Anti-dsDNA antibody response driven by histone-specific T-helper cells
- IC deposition: deposition of circulating ICs in GBM or direct binding of nucleosomal antigens to GBM followed by in situ autoantibody binding activates both complement-dependent and independent inflammatory cascades
- IC clearance:
  - ICs are normally cleared by the C1 complement complex. Binding of C1 complex to IC leads to downstream complement activation and opsonization of the IC for phagocytosis.

- C1q is a component of the C1 complex. Upon binding of C1 complex to IC, C1 complex undergoes conformational change, exposing antigenic sites of C1q, which then leads to autoantibody formation against C1q. High autoantibody titers against C1q have been suggested to correlate with active lupus.

- Inflammatory effects following impaired apoptotic bodies clearance and/or IC formations and roles of other inflammatory cells:
  - Neutrophils:
    - NETosis: a process whereby upon exposure to microorganisms, neutrophils release nuclear components, granule proteins, and chromatin to form an extracellular matrix, referred to as "neutrophil extracellular traps" (NETs) to "trap," destroy, and clear the invading microorganisms. NETs are composed of DNA and histones along with various peptides and proteinases, such as high mobility group protein box-1, cathelicidin, myeloperoxidase, neutrophil elastase, matrix metalloproteinase 9, and proteoglycan recognition protein short. NETs may serve as a source of autoantigens in systemic lupus erythematosus (SLE).
    - There are data to suggest that NETs are complement activators or can play a role in increasing C1q deposition.
  - Basophils:
    - Cross-linking of IgE to its receptors (FcεRI) on basophil surface leads to the secretion of histamine and pro-inflammatory cytokines by basophils.
    - There are data to suggest that increased titers of both dsDNA-IgE and dsDNA-IgG predict SLE disease activity better than dsDNA-IgG titers alone.
    - Activated basophils secrete cytokines (IL-4 and IL-6) and express the major histocompatibility complex class II (MHC-II) and B-cell–activating factor BAFF (also known as B-Lys), which can enhance plasma cell survival and autoantibody production amplification loop.
    - Other functions of activated basophils: promotion and regulation of TH2 adaptive immune responses, antigen presentation to T cells, plasma cell differentiation and support, monocyte polarization and recruitment, and inflammatory site organization
  - Macrophages/monocytes:

- NETs containing LL37 stimulate NLRP3 inflammasome in monocytes and result in IL-1β and IL-18 release, NETosis, and amplification of the pro-inflammatory state.
- Polymorphism in the IL-18 gene promoter with associated increased IL-18 production may promote SLE susceptibility.

- Autoreactive B and T cells due to defective regulatory mechanisms

Table A7.3 Immunosuppressive therapy for lupus nephritis class III/IV (KDIGO 2024)

Glucocorticoids *plus* any of regimens below		Comments	Treatment duration
Double therapy: GC + either MPAA or CYC			

MPAA	—	• Dosing for MPAA:
		  • MMF 1.0-1.5 g bid or
		  • Mycophenolic acid sodium 0.72-1.08 g bid
			At least 6 mo

CYC	—	• Dosing for CYC:
		  • (Euro-Lupus): 500 mg IV q2wk × 6 doses, or
		  • NIH: 0.5-1.0 g/m^2 IV monthly × 6 mo, or
		  • Oral: 1.0-1.5 mg/kg/d po (max 150 mg/d) for 2-6 mo
		• Hematologic malignancy is associated with cumulative lifetime dose >36 g.
			Up to 6 mo

Triple therapy: GC + belimumab + (MPAA or reduced-dose CYC) • Dosing for belimumab: 10 mg/kg IV q2wk for 3 doses then q4wk • Kidney benefit was most marked in patients with baseline uPCR <3 g/g. • FDA approved both IV and subcutaneous formulations; higher trough level is achieved with subcutaneous administration.			
Belimumab +	MPAA	• There is moderate evidence that adding belimumab is better than GC + MPAA alone.	Belimumab may be used up to 2.5 y in terms of safety.

Glucocorticoids *plus* any of regimens below		Comments	Treatment duration
Belimumab +	Reduced-dose CYC	• Dosing for IV CYC: 500 mg IV q2wk × 6 doses (total 12 wk) • There is moderate evidence that adding belimumab is better than GC + CYC alone.	
Triple therapy: GC + MPAA + CNI • CNI may be particularly useful in patients with high-grade proteinuria associated with extensive podocytopathy, nephrotic range proteinuria. • May consider CNI when kidney function is not severely impaired (ie, eGFR not ≤45 mL/min/1.73 m^2) • There is no data on voclosporin + CYC.			
MPAA +	CNI: Voclosporin	• Dosing for voclosporin: 23.7 mg bid • There is high certainty evidence that adding voclosporin to standard GC + MPAA is better than GC + MPAA alone.	CNI up to 3 y as long as eGFR >45 mL/min/1.73 m^2
MPAA +	CNI: Tacrolimus	• Tacrolimus (trough level ~5.5 [4-7] ng/mL) • Reduce MPAA dose in patients on tacrolimus with SCr <3.0 mg/dL • Data mainly from Chinese patients	
MPAA +	CNI: Cyclosporine	• Cyclosporine (maintenance trough level ~50-100 ng/mL) • Consider cyclosporine when voclosporin and tacrolimus are not available.	

Abbreviations: bid, twice daily; CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GC, glucocorticoid; IV, intravenous; MMF, mycophenolate mofetil; MPAA, mycophenolic acid analog; uPCR, urine protein-to-creatinine ratio.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2024 Clinical practice guideline for the management of lupus nephritis. *Kidney Int.* 2024;105(1S):S1-S69.

Table A7.4 Management of anti-glomerular basement membrane (KDIGO 2021)

Intervention	Dosing	[b]Duration of treatment

Glucocorticoids	• [a]Pulse methylprednisolone up to 1,000 mg/d × 3 consecutive days, followed by:
	  • Oral prednisone 1 mg/kg/d
	  • Reduce to 20 mg/d by 6 wk
		6 mo

Cyclophosphamide (CYC)	• 2-3 mg/kg/orally (dose adjusted to 2 mg/kg in patients >55 y); data for IV CYC are limited in terms of efficacy. • Monitor for leukopenia and adjust dose as appropriate. • Consider mycophenolate mofetil or rituximab if CYC is not tolerated. Efficacy data are limited.	3 mo
Plasma exchange (PLEX)	• 40-50 mL/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of PLEX in patients with alveolar hemorrhage and/or after kidney biopsy.	Until undetectable circulating anti-GBM antibodies, typically 14 d

Abbreviations: anti-GBM antibodies, anti-glomerular basement membrane antibodies; IV, intravenous.

[a]Glucocorticoid should be started within 24 hours prior to tissue diagnosis if high clinical suspicion due to rapidly progressive disease. Upon diagnosis confirmation, add CYC and PLEX.

[b]Maintenance therapy is not recommended. Treatment of patients without detectable anti-GBM antibodies beyond 6 months is not recommended. Advise smoking cessation whenever applicable.

Adapted from Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(1S):S1-S126, with permission from Elsevier.

A7.5 Testing Options for Monoclonal Gammopathy

- Serum (or urine) protein electrophoresis (SPEP or UPEP): SPEP separates serum proteins into five general regions in the order of albumin, α-1, α-2, β, and γ based on their charge and size. The various Ig classes (IgG, IgA, IgM, IgD, and IgE) are usually of γ mobility, but they may also be found in the β-γ and β regions, and occasionally extend into the α-2 globulin area.
- An "M"-spike indicates the presence of a "M"onoclonal protein. Each M-protein consists of two heavy polypeptide chains of the same class: γ (IgG: IgG1-IgG4), α (IgA: IgA1, IgA2), μ (IgM), δ (IgD), ε (IgE). The

paired heavy chains are associated with two light chains of the same type (κ or λ), not both.

- "Polyclonal gamma globulin" on SPEP indicates polyclonal Ig production in response to various conditions including liver disease, connective tissue, nonspecific inflammatory disorders.
- SPEP is a useful screening procedure, but it may miss a small M-protein spike or falsely identify a polyclonal increase in Ig or non-Ig as an M-protein spike. Identification of the actual makeup of the M-protein requires immunofixation. In serum (or urine) protein immunofixation electrophoresis (IFE), antibodies directed against the heavy and light chains (anti-γ, anti-μ, anti-α [IgG, M, A], and anti-κ and anti-λ) are added following the initial electrophoresis procedure to identify overproduction of any corresponding chain.
- Direct assay for serum free light chain (FLC) (Bence Jones) is more sensitive in establishing the diagnosis of monoclonal gammopathy than either SPEP or IFE. However, it must be noted that the quantity of both κ and λ light chains may be increased with poor kidney function due to reduced renal excretion. The abnormal ratio of κ to λ light chains (ie, outside the range of 0.26-1.65 for normal kidney function and 0.37-3.1 for poor kidney function) may better serve as an indicator of a monoclonal gammopathy in patients with advanced CKD.
- Serum FLC assay is particularly important in the diagnosis of nonsecretory myeloma, AL amyloidosis (patients with amyloidosis may not have active myeloma), and light-chain–only myeloma.

Table A7.6 Immunosuppressive therapy for patients with active idiopathic MPGN

See also **Table 7.10** for management strategies for MPGN.

Idiopathic MPGN	Abnormal kidney function active disease with active urine sediment, with or without nephrotic range proteinuria and no crescents
Prednisone 1 mg/kg/d (max 60-80 mg/d) × 12-16 wk →	Responders: Stabilization or improvement of GFR or ≥30% reduction in proteinuria: → Gradually taper and discontinue prednisone

	Nonresponders: → Reduce prednisone to 20 mg/d and add MMF for 6-12 mo →	Responders → Gradually taper and discontinue therapy		
		Nonresponders: → Discontinue therapy (taper off GC if applicable) → Consider repeat kidney biopsy →	Active disease: CYC 2 mg/kg/d (max 200 mg/d in adults) + prednisone 10 mg/d for 3-6 mo Or RTX 1 g q2wk × 2 doses, then repeat this 2-dose regimen in 6 mo	Nonresponders: → Discontinue therapy and provide supportive care only → Consider enrolling in clinical trials
Idiopathic MPGN	Rapidly progressive glomerulonephritis			
Methylprednisolone 1-3 g followed by oral GC taper and oral CYC regimen similar to that used for AAV (CYC 2 mg/kg/d × 3 mo, continue for a max of 6 mo based on ongoing disease activity). See also **Appendix A7.1** for GC taper.				

Abbreviations: CYC, cyclophosphamide; GC, glucocorticoid; GFR, glomerular filtration rate; max, maximum; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; RTX, rituximab.

Table A7.7 Immunosuppressive therapies for minimal change disease (KDIGO 2021)

	Immunosuppressive therapies for minimal change disease
Initial episode: If no contraindication or intolerance to GC	Prednisone or prednisolone • Dose: Prednisone 1 mg/kg/d (max 80 mg/d) or 2 mg/kg qod (max 120 mg qod) • Duration of high-dose GC: Minimum 4 wk, max 16 wk as safely tolerate • Taper over at least 24 wk after remission
Initial episode: If contraindication or intolerance to GC	• Oral CYC 2-2.5 mg/kg/d for 8 wk, *or* • Tacrolimus 0.05-0.1 mg/kg/d in divided doses for 1-2 y, *or* • Cyclosporine 3-5 mg/kg/d in divided doses for 1-2 y
Relapses: infrequent	Not yet firmly established. May consider 20-30 mg prednisone/prednisolone for a minimum of 7 d or add CYC

	Immunosuppressive therapies for minimal change disease
	(see dosing below)

Relapses:
frequent/steroid dependent
	• Oral CYC 2.0-2.5 mg/kg/d for 8-12 wk (adjust dose for leukopenia)
	Note regarding oral CYC therapy:
	• *12-wk CYC therapy duration is associated with less relapse in steroid-dependent MCD*
	• *CYC may be selected if there is no previous CYC use and no patient preference.*
	• *CYC "tends to be" associated with more durable remission rates than CNI.*
	or
	• CNIs:
	  • Cyclosporine 3-5 mg/kg/d in divided doses for 1-2 y (level 150-200 ng/mL)
	or
	• Tacrolimus 0.05-0.1 mg/kg/d in divided doses for 1-2 y (level 4-7 ng/mL)
	Notes regarding CNI therapy:
	• *After GC withdrawal, reduce CNI dose if possible.*
	• *After 1 y on CNI, attempt gradual taper and discontinuation if possible.*
	• *If CNI dependent, use the lowest dose possible. If evidence of CNI toxicity, switch to alternate therapy.*
	• *CNI therapy may be selected if patient had previously used CYC or wishes to avoid CYC.*
	or
	• Rituximab
	  • Induction regimens
	  • 375 mg/m^2 weekly for 4 doses, *or*
	  • 375 mg/m^2 × single dose; repeat after 1 wk if CD19 cells >5/mm^3, *or*
	  • 1 g/dose for 2 doses, 2 wk apart
	  • Relapse after induction
	  • 375 mg/m^2 × 1 dose, *or*
	  • 1 g IV × 1 dose
	or
	• Mycophenolic acid analog (MPAA)
	• Mycophenolate mofetil 1,000 mg bid
	• Sodium mycophenolate 720 mg bid

	Immunosuppressive therapies for minimal change disease
	Note about MPAA: After 1 y on MPAA, attempt gradual taper and discontinue if possible.

Abbreviations: bid, twice daily; CNI, calcineurin inhibitor; CYC, cyclophosphamide; IV, intravenous; MCD, minimal change disease; qod, every other day.

Adapted from Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(1S):S1-S126, with permission from Elsevier.

Table A7.8 Immunosuppressive regimens for patients with membranous nephropathy

	Dosing	Comments
Cyclophosphamide (cyclical)	• Methylprednisolone 1 g IV for 3 consecutive days at start of months 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6	In **high- or very high-risk** patients who develop deteriorating kidney function due to MN and for whom immunosuppressive therapy is felt to be appropriate, cyclical therapy with a cytotoxic agent (eg, cyclophosphamide) plus GC is the preferred initial therapy.
Cyclophosphamide (continuous)	• Methylprednisolone 1 g IV for 3 consecutive days at start of months 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1-6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d orally in months 1-6	
Rituximab (RTX)	• RTX 1 g IV administered twice within 2 wk *or* • RTX 375 mg/m^2 given 1-4 times at weekly interval	RTX is the preferred first-line immunosuppressive therapy for patients with **moderate risk** of progression.
Calcineurin inhibitors (CNIs)	Tacrolimus 0.05-0.1 mg/kg/d, trough level 3-8 ng/mL	• CNI may be considered in patients with moderate risk for disease progression in

	Dosing	Comments
	or • Cyclosporine 3-5 mg/kg/d, trough level 125-225 ng/mL	individuals with normal eGFR and RTX is not tolerated or available. • In patients with high risk of progression, add RTX after 6 mo of CNI unless negative anti-PLA2R antibody after CNI treatment. • CNI is often given in combination with prednisone 10 mg/d. Withdraw therapy if no response after 4 mo. Taper to lower levels after 12 mo. CNI may be continued for 12-24 mo, although lower relapse rate has been observed with the latter.

Abbreviations: anti-PLA2R antibody, anti-phospholipase A2 receptor antibody; GC, glucocorticoid; IV, intravenous.

A7.9 Pathogenesis of DKD

- Hyperglycemia:
  - Enhances matrix production, glycation of matrix proteins, formation of advanced glycation end products (AGE)
  - Stimulates vascular endothelial growth factor (VEGF), endothelial injury
  - Increases expression of both a profibrotic and a pro-inflammatory phenotype
- AGE:
  - AGE cross-linking with collagen
  - AGE:AGE receptor interaction (AGE:RAGE) leads to oxidative stress, activation of protein kinase C (PKC)
- Activation of PKC pathway leading to:
  - Endothelial dysfunction with decreased NO production
  - Increased expression of ET1, VEGF, nuclear factor-κB(NFκB), and PAI-1 leading to tissue inflammatory response, thrombotic microangiopathy, vascular injury
- Polyol pathway (via aldose reductase): thought to contribute to diabetic complications such as diabetic cataracts, neuropathy, hyperfiltration, albuminuria. Use of aldose reductase inhibitors has been disappointing due to hypersensitivity reactions and liver abnormalities.

- Accumulation of *N*-acetylglucosamine via hexosamine pathway: *N*-acetylglucosamine may lead to increased synthesis of TGF-β1, PAI-1.
- Prorenin activation of mitogen-activated protein kinases
- Reduction of nephrin expression presumably via angiotensin II
- Systemic and intraglomerular HTN
- Metabolic stress leading to mitochondrial dysfunction (which may lead to type B lactic acidosis observed in patients with diabetic ketoacidosis)

A7.10 Data Regarding the Effect of Glycemic Control and Albuminuria and CV Outcomes

Studies indicating that strict glycemic control decreased the risk for microalbuminuria

- Diabetes Control and Complications Trial (DCCT) (type 1 diabetes mellitus [T1D]): 9-year follow-up, intensive therapy group with mean A1C of 7% had a 35% to 45% lower risk for the development of microalbuminuria compared with control group (mean A1C 9%). Renoprotection persists even after return to less intensive therapy, a phenomenon known as "legacy effect." This is presumably due to the effect of euglycemia on long-lasting modification of transcription of genes responsible for DKD.
- Kumamoto study, (type 2 diabetes mellitus [T2D]): 60% rate reduction of microalbuminuria in relatively young patients who are nonobese with T2D in intensive group (mean A1C 7%) compared with conventional therapy group (mean A1C 9.4%)
- UK Prospective Diabetes Study (UKPDS), T2D: A1C approximately 7.0% vs 7.9%
  - Relative risk reduction for the development of microalbuminuria
  - 10-year follow-up after the study ended still revealed 24% lower risk of microvascular disease and MI. All-cause mortality also remained reduced and attributed to "legacy effect."

Strict glycemic control: effects on CVD

- Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE): intensive control (A1C 6.5% vs 7.3%) resulted in a *10% relative reduction in the combined outcome of major*

macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.

- Action to Control Cardiovascular Risk in Diabetes (ACCORD): very tight control (A1C 6.5% vs 7.5%) had *higher mortality*, up by 22% (P = .04).
- Veterans Affairs Diabetes Trial (VADT): A1C 6.9% versus 8.4%: *no difference in reduction in cardiovascular deaths or events* at 7.5-year follow-up

Table A7.11 Pharmacotherapy for patients with type 2 diabetes mellitus

Class of drugs	Benefits	Adverse effects	[a]Considerations in CKD
Biguanides (Metformin) • ↓Hepatic glucose production • ↓Intestinal glucose absorption • ↑Insulin sensitivity by ↑ peripheral glucose uptake	• Low hypoglycemic risk • Modest weight loss • Cardioprotective effect	• Lactic acidosis • Vitamin B_{12} malabsorption with resulting anemia and peripheral neuropathy (treat with B_{12} supplement)	• Stable CKD with eGFR >30: May continue • eGFR <45: Do not start • eGFR <30: Contraindicated
Glucagon-like peptide 1 receptor agonists (GLP1-RA: exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide) • Stimulate glucose-dependent insulin secretion • Suppress glucagon secretion • Reduce gastric motility • Suppress appetite	• Low hypoglycemic risk • Reduce fluctuations in fasting and postprandial glucose levels • Weight loss • Improve lipid profile and BP • [b]Improve CV outcomes: Recommended in patients with established or high ASCVD risk, obesity	• [c]Should not be used if personal or family history of medullary thyroid carcinoma or with MEN2 • Avoid use in patients with pancreatitis. • Delayed gastric emptying possible, especially with initial use	• CrCl <30 mL/min: Do not use exenatide • No dose adjustment for liraglutide, semaglutide, dulaglutide • Generally safe for eGFR >45. The use of exenatide and lixisenatide are not recommended for eGFR <30 and 15, respectively, due in part to limited clinical data.
Sodium glucose cotransporter 2 inhibitors (SGLT2i: canagliflozin,	• ↓Weight and BP • [d]Improve CV outcomes: Recommended in	• ↑Risk of urinary tract/genital mycotic infections,	• eGFR <45: Limited efficacy since SGLT2i inhibits tubular

Class of drugs	Benefits	Adverse effects	[a]Considerations in CKD
dapagliflozin, empagliflozin) • Inhibits proximal tubular glucose reabsorption via SGLT2	patients with established ASCVD risk, heart failure, CKD	Fournier gangrene • [e]Volume depletion, falls, AKI • Risk of euglycemic DKA	glucose reabsorption following glomerular filtration
Dipeptidyl peptidase 4 inhibitors (DPP4i: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) • Inhibit DPP4, thereby increasing GLP1 and other incretin hormones that stimulate glucose-dependent insulin synthesis and secretion and suppress glucagon secretion	• Low hypoglycemic risk	• May have increased risk of HF with saxagliptin and alogliptin • Use with caution in patients with a history of pancreatitis	• Generally safe • No dose adjustment for linagliptin • Dose adjustments are needed for sitagliptin and saxagliptin at eGFR <60 and 45 respectively.
Thiazolidinediones (TZD, pioglitazone) • Reduce insulin resistance	• Pioglitazone may confer ASCVD benefits.	• [f]Fluid retention (edema, HF) • ↑Fracture risk in older males and postmenopausal females	• No dose adjustment in CKD • However if significant edema, ↓dose or consider combined use with SGLT2i.
α-Glucosidase inhibitors (AGi, acarbose, miglitol, voglibose) • Inhibits the breakdown of complex carbohydrates thereby delaying their GI absorption	• Low hypoglycemic risk • ASCVD benefits suggested	• GI effects: Bloating, flatulence, diarrhea	• Use with caution in patients with CKD.

Class of drugs	Benefits	Adverse effects	[a]Considerations in CKD

Insulin secretagogues (glipizide, glyburide) and **glinides** (nateglinide, repaglinide)
• Insulin secretagogue
	• Potent A1C-lowering effect	• Hypoglycemia risk
		• Glinides have lower risk of hypoglycemia.
		• Weight gain
			• Glipizide: Dose conservatively.
			• Glyburide: Avoid use for eGFR <45.
			• Nateglinide, repaglinide:
			  • Avoid use for eGFR <15 and on dialysis.
			  • Use with caution in nondialysis patients with CKD with eGFR <30.

Colesevelam • Bile acid sequestrant	• Modestly lowers glucose • Does not cause hypoglycemia • Decreases LDL-C	• [g]↑Triglyceride levels • Not recommended in patients with gastroparesis, GI motility disorders, risk for bowel obstruction	• No dose adjustment necessary
Bromocriptine QR • ↑Hypothalamic dopamine levels and inhibits excessive CNS sympathetic tone, resulting in ↓hepatic glucose production	• Modest glucose lowering effect • Does not cause hypoglycemia • May reduce CV events	• Nausea • Orthostasis	• Renal excretion <10%; no dose adjustment necessary

GLYCEMIC CONTROL PER AACE/ACE 2020. (1) For patients with entry A1C <7.5%, start monotherapy with metformin, GLP1-RA, SLGT2i, DPP4i, *TZD, AGi, or *SU/GLN in order of preference. (2) For entry A1C >7.5%-9.0% or >9% without symptoms (eg, polydipsia, polyuria, weight loss), use dual therapy for 3 mo with metformin + one of the following: GLP1-RA, SGLT2i, DPP4i, *TZD, *U/GLN, *basal insulin, colesevelam, bromocriptine QR, or AGi in order of preference. (3) If goal A1C is not achieved after 3 mo of dual therapy, add a third agent from: GLP1-RA, SGLT2i, *TZD, *SU/GLN, *basal insulin, DPP4i, colesevelam, bromocriptine QR, or AGi in order of preference. (4) Add insulin if goal A1C is not achieved after 3 mo of triple therapy. (5) For entry A1C >9% with symptoms, initiate insulin with or without other agents. *Use these agents with caution.

Abbreviations: AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GI, gastrointestinal tract; HF, heart failure.

[a]Units for eGFR is mL/min/1.73 m^2.

[b]GLP1-RA: Strongest evidence for liraglutide > semaglutide > exenatide extended release.

[c]Liraglutide has been shown to stimulate calcitonin release and lead to hyperplasia of thyroid gland C cells and tumors in rodent model.

[d]SGLT2i: Evidence is modestly stronger for empagliflozin > canagliflozin.

[e]The American Association of Clinical Endocrinologists/American College of Endocrinology Scientific and Clinical Review expert consensus group recommend holding SGLT2i 24 to 48 hours prior to stressful activities (eg, surgeries, extreme sports) and for patients on both SGLT2i and insulin to avoid very low-carbohydrate meals and excess alcohol intake.

[f]Contraindicated in the New York Heart Association functional classes III and IV or hepatic impairment.

[g]Contraindicated for patients with triglyceride levels greater than 500 mg/dL.

A7.12 The Use of ACEi Versus ARB in DKD

- Renin-angiotensin-aldosterone system (RAAS) inhibition with either ACEi or ARB confers renoprotection in patients with DKD, independent of BP control via both intraglomerular hemodynamic and nonhemodynamic (ie, antiproliferative and antifibrotic) effects of angiotensin II.
- RAAS inhibition also blocks aldosterone, which, in turn, reduces sodium retention, potassium and magnesium wasting, and tissue inflammation and fibrosis. 40% to 50% of patients on ACEi or ARB develop an "aldosterone escape" by 12 months of therapy. Addition of aldosterone antagonism may be considered if indicated and safely tolerated.
- Data on T1D
  - RAAS inhibition does not reduce the progression from normoalbuminuria to microalbuminuria.
  - ACEi reduces the risk of progression from microalbuminuria to overt nephropathy.
  - In *normotensives* with microalbuminuria, ACEi leads to a 60% reduction in progression to macroalbuminuria and 3 times likelihood in regression to normoalbuminuria.
  - Captopril treatment in patients with macroalbuminuria or overt nephropathy reduces albuminuria and GFR decline and delays the onset of kidney failure.

    - Similar data for ARB are not as robust as those for ACEi, but their clinical effects are expected to be similar to ACEi.
- Data on T2D
    - Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study (IRMA 2) trial: Irbesartan reduces progression to overt DKD by 70% in patients with hypertensive type 2 over 2-year follow-up.
    - Microalbuminuria Reduction with Valsartan in Patients with T2D (MARVAL) trial: Daily valsartan 80 mg reduces urinary albumin excretion better than amlodipine (44% vs 8%).
    - Irbesartan Diabetic Nephropathy T (IDNT) and Reduction in Endpoints in NIDDM with the Ang II Antagonist Losartan (RENAAL) trials: T2D with macroalbuminuria and reduced GFR, ARBs reduce proteinuria and composite end points of death, dialysis, and doubling of SCr.

NOTE: In contrast to T1D, data on the efficacy of ACEi in type 2 DKD are not as robust.

CHAPTER 8: TRANSPLANT IMMUNOBIOLOGY

A8.1 Molecular Typing of Human Leukocyte Antigen B (HLA-B) and HLA-DR

- HLA-B antigens are distinguished by either the immunogenic Bw4 or Bw6 epitope encoded on this antigen between amino acids 77 and 83.
- The *DRB3*, *DRB4*, or *DRB5* gene encodes HLA-DR52, HLA-DR53, and HLA-DR51, respectively. Some *HLA DRB1* genes are commonly linked to one of these additional *DRB345* genes. For example, DR17 is commonly linked to DR52; DR7 is commonly linked to DR53; DR15 is commonly linked to DR51. However, DR8, and members of the DR1 group, is not commonly linked to a DRB345 antigen (**Figure A8.1**).

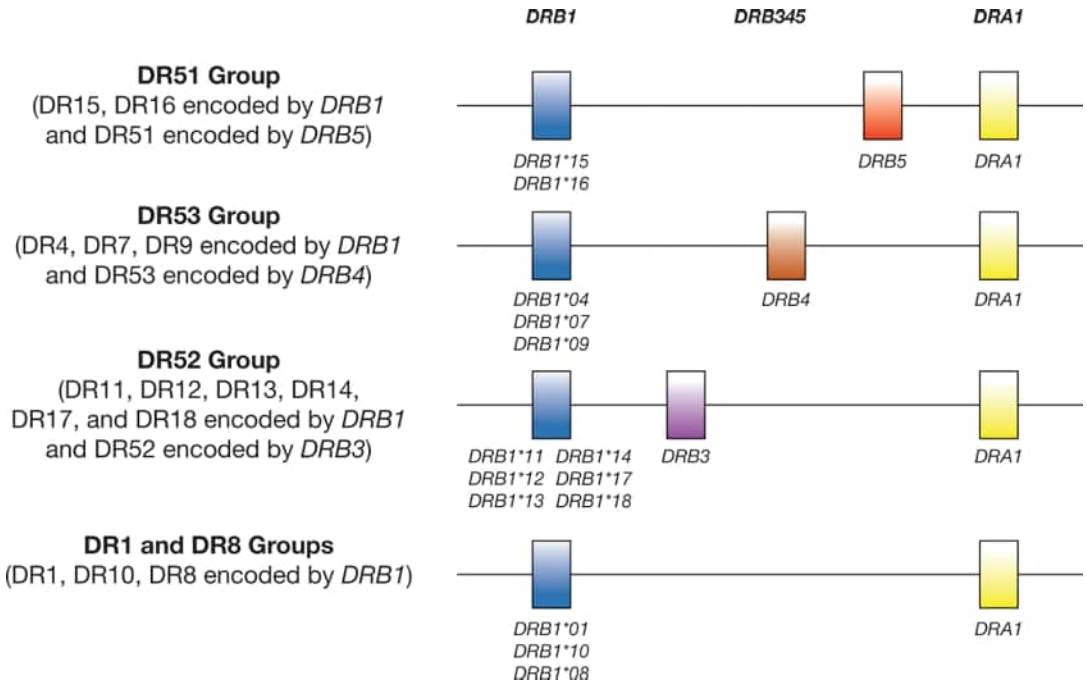


FIGURE A8.1 HLA-DR genomic region. Most *DRB1* genes are associated with a *DRB3, DRB4,* or *DRB5* gene. The *DRB345* genes encode the DR52, DR53, and DR51 antigens, respectively. The DR51 group includes the DR15 and DR16 antigens (encoded by the *DRB1* gene depicted in teal [blue green]) that are commonly associated with the DR51 antigen (encoded by the *DRB5* gene). Antigens in the DR1 and DR8 groups (DR1, DR10, and DR8) are not commonly associated with a *DRB345* gene. The majority of polymorphisms in DR antigens are encoded in the *DRB1/345* genes (such as DR15, DR51, or DR1). The protein translated from these genes is noncovalently bound to the protein produced by translation of the *DRA1* gene (depicted in yellow).

A8.2 Modifications of the Single-Antigen Bead Assay

NOTE

Readers must have basic knowledge about the concept of antibody excess and prozone effect.

- One limitation of the single-antigen bead assay is the limited dynamic range of the Luminex analyzer that results in the inability to accurately assess the strength of strong antibodies.
  - Single-antigen testing with serum dilution can, therefore, be used to aid in interpretation of results when antibody-to-bead reactivity is in the range of saturation for a Luminex analyzer (generally >15,000 mean fluorescence intensity [MFI]). Retesting of diluted sera can

more accurately assess the strengths of strong antibodies that are saturating single-antigen beads.

  - Example: An antibody identified at baseline to A2 in the single-antigen bead test at 18,000 MFI in undiluted sera may appear unchanged after serial rounds of plasmapheresis (10,500 MFI; **Table A8.1**). However, single-antigen testing of the baseline and postplasmapheresis samples with dilution may show that the same antibody in the postplasmapheresis sample was significantly less strong at 2,500 MFI (see **Table A8.1**). A significant change in the single-antigen bead test is considered to be at least a 50% change in MFI. (The C1q modification of the single-antigen bead test is discussed below.)

- Another noted limitation of the single-antigen bead assay is false-negative, or falsely low, antibody strength due to antibody excess. This phenomenon is referred to as *prozone*.
  - False-negative/low antibody strength is identified when the results of testing methods do not correlate to one another. For example, single-antigen bead testing identified a weak antibody, but that same sera tested by another method identified a strong antibody.
  - Single antigen with serum dilution, or single-antigen C1q testing can be used as a supplementary method to rule out prozone (discussed below).
- Single-antigen C1q:
  - The single-antigen C1q test is a modification of the single-antigen class I and class II Luminex assay that detects the ability of HLA antibodies to bind C1q (the first component of the classic complement cascade) after incubation with Luminex beads. The presence of bound complement is detected using a fluorescent-conjugated anti-C1q antibody. The C1q-binding assay enables characterization of strong antibodies that are potentially able to fix complement in the complement-dependent cytotoxicity (CDC) assay.
  - Antibodies first identified to be weak/moderate in strength in the single-antigen bead test and significantly stronger after serum dilution, or positive in the single-antigen C1q test indicate antibody excess (prozone) or interference in the first test. Importantly, the single-antigen C1q test is generally performed on undiluted serum.

- Example: An antibody to A68 is identified at 8,500 MFI in the single-antigen bead test (see **Table A8.1**). Dilution of the serum at 1:10 shows the strength of the antibody to be much stronger (15,000 MFI) and C1q positive in the modification of the test. Taken together, these results indicate that the serum displays evidence of antibody excess (prozone) or interference and, in actuality, the antibody to A68 is much stronger than 8,500 MFI. In this example, after repeated rounds of plasmapheresis-based desensitization therapy, the strength of the A68 antibody is identified at 16,000 MFI in undiluted serum. Dilution of the serum does not result in a significant change in MFI (13,000 MFI), and the antibody remains C1q positive. There is no longer evidence of antibody excess or interference in the serum, and the antibody is still very strong, indicating that the antibody removal therapy has not significantly affected the strength of this antibody.

Table A8.1 Single-antigen bead-antibody assessment with serum dilution and C1q testing

HLA	Baseline serum			Post-plasmapheresis serum		
	Undiluted	Diluted 1:10 MFI	C1q	Undiluted	Diluted 1:10 MFI	C1q
A2	18,000	14,000	Positive	10,500	2,500	Negative
A68	8,500	15,500	Positive[a]	16,000	13,000	Positive

Abbreviations: HLA, human leukocyte antigen; MFI, mean fluorescence intensity.

[a]Testing of this baseline sera indicates antibody excess (prozone) or interference of A68 antibody in the undiluted serum.

CHAPTER 9: KIDNEY TRANSPLANTATION

A9.1 Long-Term Mortality in Obese Living Kidney Donors

- Scientific Registry of Transplant Recipients database (n = 119,769 living kidney donors with a maximum follow-up of 20 years)
  - Obese living kidney donors (body mass index [BMI] ≥30) were found to have a 30% increased risk of long-term mortality compared with their nonobese counterparts (adjusted hazard ratio: 1.32, P = .006).
  - Study limitations:
    - Of the 119,769 living kidney donors, BMI data at donation were only available in approximately two-thirds of the study cohort (n =

78,592). Multiple imputation was used for one-third of the cohort with missing BMI data at donation.
    - Lack of data on predonation metabolic syndrome
    - Lack of data on postdonation development of other comorbidities, such as HTN, diabetes, or CVD

A9.2 Impact of Age on Long-Term Safety

- Study design: single-center study: *N* = 539 consecutive live kidney donors (422 donors were <60 years and 117 were 60 years or above). Older donors had lower mean predonation GFR (80 vs 96 mL/min/1.73 m^2), higher BMI, and higher American Society of Anesthesiologist (ASA) classification compared with younger donors.
- Results:
    - There was no difference in the mean maximum decline in eGFR between the two groups at a median follow-up of 5.5 years (maximum decline in eGFR was 38% ± 9%).
    - The percentage maximal decline was comparable between the two groups.
    - At 5 years follow-up, significantly more older patients had an eGFR of less than 60 mL/min/1.73 m^2 compared with younger donors (94% vs 80%, $P < .001$). However, renal function stabilized during follow-up, and no donor had an eGFR of less than 30 mL/min/1.73 m^2.
- Conclusion: After kidney donation, decline in eGFR is similar in younger and older donors. As kidney function does not progressively decline, live kidney donation by older patients is considered safe.

A9.3 Association Between Living Kidney Donation, Race, HTN, and eGFR

- Study design: longitudinal multicenter study of 1,295 living kidney donors. Controls: *n* = 8,233 healthy nondonors drawn from the ARIC and CARDIA studies (ARIC: Atherosclerosis Risks in Communities; CARDIA: Coronary Artery Risk Development in Young Adults). Median follow-up: 6 years
- Results:

  - Black race was associated with a 27% higher risk of HTN, regardless of whether the individual donated a kidney. Although the baseline risk of HTN was higher for Blacks, donation was associated with a 19% higher risk of HTN compared with healthy nondonor controls, regardless of race (White or Black).
  - Although kidney donors experienced an increase in eGFR over time after donation (attributed to adaptive hyperfiltration), their eGFR plateaued after they developed HTN.
- Conclusion: The study finding suggests that incident HTN adversely affects GFR after kidney donation.
- Study limitations: Factors that might impact the effect of HTN on eGFR such as BP control, quality of care for subjects with HTN, and use of antihypertensive medications were not assessed.

Table A9.4 Immunosuppression reduction strategies in kidney transplant recipients with BKPyV-DNAemia with or without BKPyV-nephropathy (opinion based)

Common practice: reduction or discontinuation of antimetabolite first

- Decrease or hold mycophenolic acid (MFA) derivatives (or azathioprine).
- Monitor BKPyV-DNA every 2-4 wk to assess dynamics and response to intervention.
- If BKPyV load does not decrease by 10-fold or increases, consider discontinuing antimetabolites if not already done.
- Continue to monitor BKPyV-DNA every 2-4 wk.
- If further immunosuppression reduction is necessary, consider lowering calcineurin inhibitor (CNI) target goal levels (consider monitoring DSA, particularly in high immunologic risk patients).
- Continue to monitor BKPyV-DNA every 2-4 wk until clear.
- Currently existing literature does not support the use of leflunomide, cidofovir, quinolones, or intravenous immunoglobulin (IVIG). However, may consider IVIG if DSA is present (or if histopathologic findings on biopsy are indistinguishable from those of acute rejection).

Less common practice: reduction in CNI dose first (lower target goal)

- Lower CNI target goal by 20%-30%.
- Monitor BKPyV-DNA every 2-4 wk to assess dynamics and response to intervention.
- If BKPyV-DNA does not decrease by 10-fold or increases, consider further lowering CNI target goal levels (consider monitoring DSA, particularly in high immunologic risk patients).
- Continue to monitor BKPyV-DNA every 2-4 wk.
- If further immunosuppression reduction is necessary, consider reduction or discontinuation of antimetabolites.
- Continue to monitor BKPyV-DNA every 2-4 wk until clear.
- As above, may consider IVIG if DSA is present (or if histopathologic findings on biopsy are indistinguishable from those of acute rejection)

For kidney transplant recipients on belatacept-based regimen

- Decrease or hold MFA derivatives (or azathioprine).
- Monitor BKPyV-DNA every 2-4 wk to assess dynamics and response to intervention.
- If BKPyV load does not decrease by10-fold or increases, consider discontinuing antimetabolites if not already done.
- Continue to monitor BKPyV-DNA every 2-4 wk.
- If further immunosuppression reduction is necessary, consider increasing the interval of belatacept administration to every 6 wk (consider monitoring DSA, particularly in high immunologic risk patients).
- Continue to monitor BKPyV-DNA every 2-4 wk until clear.
- In refractory cases, consider switching to low dose CNI or mTOR inhibitor-based regimen (evidence-based recommendations are lacking).
- May consider IVIG if DSA is present (or if histopathologic findings on biopsy are indistinguishable from those of acute rejection)

Abbreviation: DSA, donor-specific antibody.

A9.5 mTOR Inhibitor in Post-Transplant Cutaneous Malignancies

- The Sirolimus Renal Conversion Trial (CONVERT) in which patients were randomized to sirolimus conversion or calcineurin inhibitor (CNI) continuation demonstrated that:
  - Sirolimus-based, CNI-free immunosuppression was associated with a significant reduction in non-melanoma skin cancers at 2 years postconversion (1.2 vs 4.3, $P < .001$).
  - Sirolimus-treated patients had a significantly lower incidence of melanoma, although the incidence of melanoma was low (1.1% in the CNI continuation group and 0% in the sirolimus conversion group, $P = .06$).
  - There was a nonstatistically significant lower rate of all other cancers (1.0 vs 2.1, $P = .058$).

Table A9.6 Incidence of EBV-associated PTLD by PTLD subtypes and time of onset after transplant

PLD subtypes	EBV association	Onset after transplant
Early lesions	Almost 100% EBV positive	Most early PTLD
Polymorphic PTLD	>90% EBV positive	Variable

PLD subtypes	EBV association	Onset after transplant
Monomorphic PTLD	Both EBV positive and EBV negative	• EBV positive: Most occur within the first 3 y after transplantation • EBV negative: Late-occurring PTLD (>5 y after transplant)
Hodgkin lymphoma-like PTLD	>90%	

Abbreviations: EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disorder.

A9.7 Suggested Post-Transplant Lymphoproliferative Disorder (PTLD) Treatment Algorithm/Treatment Modalities

Reduction or discontinuation of immunosuppression

- Immunosuppression reduction to restore Epstein-Barr virus (EBV)-specific cellular immunity should be the first line of treatment.
- The antimetabolites azathioprine or mycophenolic acid derivatives are generally discontinued, although their use has not been consistently demonstrated to increase PTLD risk. A lower or no increased risk has been observed. Nonetheless, it is common practice to discontinue the antimetabolites because of the theoretical risk of net protumor effect of overimmunosuppression.
- CNI dose reduction by 50% to 75% at the discretion of the clinician. Prednisone can be continued to prevent allograft rejection. For critically ill patients, those with monoclonal tumors or extensive disease, immunosuppression should be drastically reduced or discontinued.
- Patients with polyclonality are most likely to respond to immunosuppression reduction.
- EBV negative is less responsive to immunosuppression reduction alone than EBV-positive disease.
- Suggested factors predictive of a poor response to reduction in immunosuppression alone include:
  - Elevated lactate dehydrogenase, organ dysfunction at diagnosis, multiple organ involvement, bulky disease (largest tumor deposit >7

cm in diameter), advanced stage (Ann Arbor stage III or IV), and older age (>50 years)
    - Other poor prognostic factors include: World Health Organization (WHO) performance status score of 3 or 4 (a score of 3 is defined as confined to bed or a chair for >50% of waking hours, and a score of 4 as completely disabled), late onset of disease (>1 year after transplant), central nervous system disease, severe organ dysfunction, AKI at diagnosis, and T-cell disease
- Restaging should be performed 2 to 4 weeks after immunosuppression reduction.

Failure to respond to immunosuppression reduction alone

- RTX, a chimeric monoclonal antibody targeting CD20 on the surface of B cells, is currently considered a standard therapy for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone (recommended dose: RTX at 375 mg/m^2 body surface area weekly for 4 weeks. Extended treatment with four additional doses may increase complete response rate).
- Chemotherapy:
    - Indicated in patients refractory to reduction in immunosuppression and/or RTX, in those with aggressive disease at presentation, and in those not amenable to surgery
    - Other indications: peripheral T-cell lymphoma, Hodgkin lymphoma, Burkitt lymphoma, primary central nervous system lymphoma, and other uncommon lymphoma. All CD20-positive subtypes should also receive RTX.
    - **C**yclophosphamide, **H**ydroxydaunorubicin or doxorubicin, **O**ncovin or vincristine, **P**rednisone **(CHOP)**-based chemotherapy is the most widely use regimen. Currently, reduced immunosuppression and risk-stratified sequential treatment with RTX followed by CHOP (a.k.a. R-CHOP) is considered standard of care for polymorphic and monomorphic diffuse large B-cell lymphoma-like PTLD, irrespective of EBV status (RTX at 375 mg/m^2 weekly for 4 weeks, followed by CHOP every 3 weeks with granulocyte-stimulating factor support).

Table A9.8 Post-transplantation lymphoproliferative disorder (PTLD) treatment modalities

Treatment	Indications	Comments
Immunosuppression reduction	Mainstay of therapy in all PTLD subtypes	
Rituximab	First-line treatment for CD20-positive PTLD not responsive to IS reduction alone	
Chemotherapy	• For those who fail to achieve complete remission despite IS reduction and rituximab therapy • Currently, IS reduction and risk-stratified sequential treatment with rituximab followed by CHOP (a.k.a. R-CHOP) are considered standard of care for polymorphic and monomorphic diffuse large B-cell lymphoma. • Other indications: Aggressive disease at presentation, lesions not amenable to surgery, among others	CHOP-based therapy is the most widely used regimen. Increased infectious risk G-CSF use may decrease morbidity and mortality.
Surgery	• For localized disease in conjunction with IS reduction • Palliative care (symptomatic relief)	
Radiation therapy	• For localized disease in conjunction with surgery and IS reduction • Palliative care (symptomatic relief)	
Antiviral therapy	Acyclovir and ganciclovir are of unproven benefit because their activity is dependent on intracellular phosphorylation by virally coded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase.	Some centers continue to use antiviral therapy based on limited studies suggesting that lytic viral DNA (not just latent viral DNA) is also present in established PTLD.
mTOR inhibitors	Insufficient data to recommend or refute its use in the treatment of PTLD	
Adoptive immunotherapy (adoptive transfer of EBV-specific cytotoxic T cells)	• Relapsed or refractory PTLD • Preemptive therapy	EBV-positive PTLD only Expensive, not readily available, time-consuming

Treatment	Indications	Comments
Retransplantation	Should be disease free for at least 2 y prior to retransplantation (see **Table 9.3**). Consultation with Hematology/Oncology recommended.	

Abbreviations: CHOP, cyclophosphamide, hydroxydaunorubicin or doxorubicin, oncovin or vincristine, prednisone; G-CSF, granulocyte-colony stimulating factor; IS, immunosuppression.

Detailed discussion is beyond the scope of this chapter. Interested readers are referred to reference Pham P-CT, Pham P-TT. *Quick Guide to Kidney Transplantantation*. Wolters Kluwer, Inc; 2020.

CHAPTER 10: PHARMACOLOGY

None.

CHAPTER 11: ACUTE KIDNEY INJURY AND INTENSIVE CARE UNIT (ICU) NEPHROLOGY

Table A11.1 Classification and staging of acute kidney injury

	Serum creatinine			Urine output
Stage	AKIN[a]	KDIGO (2012)	RIFLE[b]	All
1	↑SCr 1.5-2.0 × baseline or ↑SCr by ≥0.3 mg/dL within 48 h	↑SCr 1.5-1.9 × baseline within 7 d or ↑SCr by ≥0.3 mg/dL within 48 h	**R**ISK ↑SCr ≥1.5 × baseline or ↓GFR >25%	<0.5 mL/kg/h for 6-12 h
2	↑SCr >2.0-3.0 × baseline	↑SCr ≥2.0-2.9 × baseline	**I**NJURY ↑SCr ≥2.0-3.0 × baseline or ↓GFR >50%	<0.5 mL/kg/h for ≥ 12 h
3	↑SCr 3.0 × baseline or or ↑SCr to ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or acute initiation of KRT	↑SCr ≥3.0 × baseline or ↑ in SCr to ≥4.0 mg/dL or initiation of RRT	**F**AILURE ↑SCr >3.0 × baseline or ↓GFR >75% ↑SCr to ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL	<0.3 mL/kg/h for ≥ 24 h or anuria for ≥12 h
			LOSS	

	Serum creatinine			Urine output
Stage	AKIN[a]	KDIGO (2012)	RIFLE[b]	All
			Complete loss of kidney function for >4 wk	
			ESKD KRT for >3 mo	

Abbreviations: AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, renal replacement therapy; RIFLE, Risk Injury Failure Loss End-stage Kidney Disease; SCr, serum creatinine.

[a]AKIN: SCr values as defined are measured following fluid resuscitation.

[b]RIFLE: If no baseline SCr is available, assume an SCr equivalent to eGFR (MDRD) of 75 mL/min/1.73 m^2.

Adapted from Section 2: AKI definition. *Kidney Int Suppl*. 2012;2(1):19-36. Accessed July 16, 2024. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf, with permission from Elsevier.

CHAPTER 12: CONTINUOUS KIDNEY REPLACEMENT THERAPY

None.

APPENDIX B: Supplemental Study Materials on Acid-Base Disorders

SUPPLEMENTAL STUDY MATERIALS

S2.1 Diagnosing Acid-Base Disorders

In determining acid-base disorders from a blood gas and chemistry, the following are defined as normal values: pH = 7.4, P_{CO_2} = 40 mm Hg, tCO_2 (herein referred to as $[HCO_3^-]$ to avoid confusion with P_{CO_2}) = 24 mmol/L, serum anion gap (SAG) = 12 mmol/L

Four BASIC STEPS in the assessment of acid-base disorders

Step 1: Check serum $[HCO_3^-]$ to determine two different acid-base disorder possibilities.

- For $[HCO_3^-]$ less than 24 → Either metabolic acidosis OR respiratory alkalosis (acute or chronic) is possible.
- For $[HCO_3^-]$ greater than 24 → Either metabolic alkalosis OR respiratory acidosis (acute or chronic) is possible.

Step 2: Check pH to determine which of two possibilities in step 1 is most likely. Steps 1 and 2 together help determine the FIRST acid-base disturbance.

Example: For a patient with serum $[HCO_3^-]$ 20 mmol/L, either metabolic acidosis or respiratory alkalosis is possible.

- If serum pH is 7.5, respiratory alkalosis is more likely than metabolic acidosis.
- If, however, serum pH is 7.3, metabolic acidosis is more likely.

Step 3: Calculate the expected compensation for the FIRST acid-base disturbance above, then compare the expected to the actual

value. A mismatch indicates the presence of a SECOND acid-base disturbance:
Compensation factors:

	$\Delta[HCO_3^-]$	ΔP_{CO_2}
[a]**Metabolic** acidosis	↓**1**	↓1
Metabolic alkalosis	↑**1**	↑0.7
[b]**Respiratory** acidosis (acute)	↑0.1	↑**1**
Respiratory acidosis (chronic)	↑0.4	↑**1**
Respiratory alkalosis (acute)	↓0.1	↓**1**
Respiratory alkalosis (chronic)	↓0.5	↓**1**

[a]For severe metabolic acidosis, that is, serum $[HCO_3^-]$ <10 mmol/L, use Winter's formula to calculate the expected PCO_2. Winter's formula calculates the "expected PCO_2," NOT ΔPCO_2.

[b]Compensation factors vary slightly in the literature. Overall, however, if a margin of error of ±2 mmol/L for HCO_3^- and ±3 mm Hg for PCO_2 are allowed, acid-base disorders calculated will all be relatively similar.

Winter's formula: Expected P_{CO_2} = (1.5 × serum $[HCO_3^-]$) + 8 ± 2 mm Hg
Applying Winter's formula: A patient with metabolic acidosis and serum $[HCO_3^-]$ of 10 mmol/L would have an expected P_{CO_2} of 1.5 × 10 + 8 ± 2 = 23 ± 2 mm Hg.
Example 1: Patient with [HCO_3^-] 36 mmol/L, pH 7.57, P_{CO_2} 40 mm Hg. What are the acid-base disorders?

- *Steps 1 and 2: Check [HCO_3^-] and pH: Based on the high [HCO_3^-] and pH, the FIRST acid-base disturbance is metabolic alkalosis.*
- *Step 3: Calculate compensation. Compare the expected to the actual value to determine the presence of second acid-base disturbance.*
  - *Expected compensation for metabolic alkalosis: For every 1 increase in [HCO_3^-], there is a 0.7 increase in P_{CO_2}.*

- *Since there is a 12 increase in [HCO_3^-] in current patient, there should be a 0.7 × 12 = 8.4 increase in P_{CO_2}.*
- *The expected P_{CO_2} should be 40 + 8.4 or ~ 48 ± 3 mm Hg.*
- *Compare to actual value: The actual P_{CO_2}, is 40 mm Hg, a value much lower than the expected 48.*
- *This means the patient also has a respiratory alkalosis as a SECOND acid-base disturbance.*

Example 2: Patient with [HCO_3^-] 16 mmol/L, pH 7.45, P_{CO_2} 24 mm Hg.

- *Steps 1 and 2: Check [HCO_3^-] and pH: Based on the low [HCO_3^-] and high pH, the FIRST acid-base disturbance is respiratory alkalosis.*
- *Step 3: Calculate compensation. Compare the expected to the actual value to determine the presence of second acid-base disturbance:*
  - *Expected compensation for respiratory alkalosis (acute): For every 1 decrease in P_{CO_2}, there is a decrease of 0.1 in [HCO_3^-].*
  - *Since there is a decrease of 16 in P_{CO_2}, there should be a decrease in [HCO_3^-] of 0.1 × 16 = 1.6 ~ 2. The expected [HCO_3^-] for acute respiratory alkalosis is 24 − 2 = 22 ± 3 mm Hg.*
  - *Expected compensation for respiratory alkalosis (chronic): For every 1 decrease in P_{CO_2}, there is a decrease of 0.5 in [HCO_3^-].*
  - *Since there is a decrease of 16 in P_{CO_2}, there should be a decrease in [HCO_3^-] of 0.5 × 16 = 8.0. The expected [HCO_3^-] for chronic respiratory alkalosis is 24 − 8 = 16 ± 2 mmol/L.*
  - *Since the actual [HCO_3^-] is 16, it is likely that the patient just has a chronic respiratory alkalosis and no "SECOND" acid-base disturbance based on compensation calculations.*

Step 4: Check SAG to determine the presence of a THIRD acid-base disorder:

- Derivation and definition of SAG:

Total positive charges = Total negative charges

$$[Na^+] + [\text{unmeasured cations}^+] = [Cl^-] + [HCO_3^-] + [\text{unmeasured anions}^-]$$

Rearranging the equation above,

$$[Na^+] - [Cl^-] - [HCO_3^-] = [\text{unmeasured anions}^- - \text{unmeasured cations}^+]$$

The difference [unmeasured anions$^-$ – unmeasured cations$^+$] is defined as serum anion gap (SAG).
A normal SAG as defined above ([Na^+] – [Cl^-] – [HCO_3^-]) is approximately 12 ± 2 (may vary slightly from institution to institution).

- Interpretation of increased SAG:

Case: Imagine a patient with an SAG = 27. This may be interpreted as having 12 normal SAG and 15 excess anions$^-$ (A^-):

- 27 = 12 normal AG + 15 A^-
- One can assume that the excess 15 anions$^-$ detected is accompanied by 15 acid H^+.

  15 HA 15 H^+ + 15 anions$^-$
- Assume that for every H^+, one HCO_3^- will be consumed. In this case, 15 HCO_3^- will be consumed.
- Expected [HCO_3^-] would thus be = 24 – 15 = 9 mmol/L. This is the *expected* [HCO_3^-] based on the detected excess anions$^-$.
- Compare the calculated *expected* [HCO_3^-] to the measured *actual* serum [HCO_3^-]:
  - If the actual serum [HCO_3^-] = expected [HCO_3^-] ± 2, there is no other acid-base process.
  - If the actual serum [HCO_3^-] is greater than the expected [HCO_3^-], there are actually more [HCO_3^-] than expected. This implies the patient **also** has metabolic alkalosis.

- If the actual serum [HCO_3^-] is less than the expected [HCO_3^-], there are actually less [HCO_3^-] than expected. This implies there is "some other process" that is consuming [HCO_3^-] but is not contributing any anions for detection on SAG. This implies the patient **also** has a non-AG metabolic acidosis.

Case: Imagine another patient with an SAG = 25. This may be interpreted as having 12 normal SAG and 13 excess anions$^-$ (A^-):

- 25 = 12 normal AG + 13 A^-
- One can assume that the excess 13 anions$^-$ detected is associated with 13 acid H^+.

  13 HA 13 H^+ + 13 anions$^-$
- Assume that for every H^+, one HCO_3^- will be consumed. In this case, 13 HCO_3^- will be consumed.
- Expected [HCO_3^-] is calculated to be = 24 – 13 = 11 mmol/L. This is the *expected* [HCO_3^-] based on the detected excess anions$^-$.
- Compare the calculated *expected* [HCO_3^-] of 11 mmol/L to the measured *actual* serum [HCO_3^-].
  - If the patient's actual serum [HCO_3^-] = 25 mmol/L, it would mean the patient **also** has a metabolic alkalosis in addition to the high AG metabolic acidosis.
  - If the patient's actual [HCO_3^-] = 5, it would imply the patient also has another metabolic acidosis process that is using up the HCO_3^-, but this acid does not have an accompanying anion that could be detected in the AG. This implies that the patient **also** has a **normal AG** metabolic acidosis in addition to the high AG metabolic acidosis.

NOTE

Although we typically assume a 1:1 ratio of acid consumption of HCO_3^-, this ratio is slightly higher for organic acids. For lactic acidosis, this ratio is 1.6 lactate:1.0 HCO_3^- due to the buffering of lactic acid by molecules other than [HCO_3^-] (eg,

bones, intracellular buffers). That is, for every 1.6 mmol of lactate, only one HCO_3^- will be consumed, not 1.6 HCO_3^-.

Example: In a patient with an increased SAG of 29 due to lactate acidosis, one would expect the HCO_3^- *to drop by (29 – 12)/1.6 = 11 instead of (29 – 12) = 17. The expected* HCO_3^- *would be 24 – 11 = 13, not 24 – 17 = 7.*

- Hint in solving acid-base problems: Always follow steps 1 through 4. Do not skip any step. Even if compensation calculation in step 3 does not indicate the presence of a second acid-base disorder, go on to step 4 and calculate SAG. This last step may uncover another acid-base disorder.

Practice acid-base problems

Unless otherwise specified, units for electrolytes are mmol/L.

Case: A 48-year-old female with a 3- to 4-month history of nausea, diarrhea, poor appetite, insomnia, and overall decreased energy level.

Blood chemistry: [Na^+] 132, [K^+] 4.2, [Cl^-] 105, [HCO_3^-] 10, blood urea nitrogen (BUN) 77 mg/dL, serum creatinine (SCr) 7.8 mg/dL. Blood gas: pH 7.18, P_{CO_2} 28 mm Hg. What is/are the acid-base disturbance(s)?

Steps 1 and 2: Low **[HCO_3^-] and** low **pH** → "FIRST" process is metabolic acidosis.

Step 3: Compensation:	Δ[HCO_3^-]	ΔPCO_2
Metabolic acidosis	↓1	↓1

For the current case, ↓[HCO_3^-] by 14, P_{CO_2} thus ↓by 14 × 1 = 14 → expected P_{CO_2} = 40 – 14 = 26 ± 3, which is within the range of actual P_{CO_2} of 28 → no "SECOND" process.

Step 4: SAG = 17 → 12 normal AG + 5 anions → 5 anions must have accompanied 5 H^+ ions, which are expected to consume 5 [HCO_3^-] → expected [HCO_3^-] = 24 – 5 = 19 ± 2. The actual [HCO_3^-] is 10, which is much less than 19, suggesting something

else is using up the bicarbonate, but not showing up in the AG. This means the patient also has a normal AG metabolic acidosis.

Answer: Elevated SAG and normal AG metabolic acidosis. The former is likely due to kidney failure, and the latter possibly due to diarrhea. The high SAG associated with kidney failure is due to the accumulation of organic anions such as sulfates, phosphates, and urates seen with reduced glomerular filtration.

Case: An 85-year-old male with a history of rheumatoid arthritis who presents with dizziness and tinnitus.

Blood chemistry: [Na^+] 135, [K^+] 4.1, [Cl^-] 99, [HCO_3^-] 12, BUN 6 mg/dL, SCr 0.7 mg/dL. Blood gas: pH 7.36, P_{CO_2} 22 mm Hg. What is/are the acid-base disturbance(s)?

Steps 1 and 2: Low **[HCO_3^-] and** low **pH** → "FIRST" process is metabolic acidosis.

Step 3: Compensation:	$\Delta[HCO_3^-]$	ΔPCO_2
Metabolic acidosis	↓1	↓1

For the current case, ↓[HCO_3^-] by 12, P_{CO_2} also ↓by 12 × 1= 12 → expected P_{CO_2} = 40 − 12 = 28 ± 3, which is higher than the actual P_{CO_2} of 22 → "SECOND" process: respiratory alkalosis.

Step 4: SAG = 24 → 12 normal AG + 12 anions → 12 anions must have accompanied 12 H^+ → These 12 H^+ ions are expected to consume 12 [HCO_3^-] → expected [HCO_3^-] = 24 − 12 = 12 ± 2, which is within the range of actual [HCO_3^-] of 12 → No "THIRD" process.

Answer: High SAG metabolic acidosis and respiratory alkalosis, likely due to excess salicylate ingestion. Other possible scenarios with similar findings: respiratory alkalosis from acute pulmonary embolism or pneumonia and concurrent high SAG from chronic acetaminophen use (accumulation of oxoproline a.k.a. pyroglutamic acid).

Case: A 32-year-old woman found unresponsive in the subway.

Blood chemistry: [Na^+] 127, [K^+] 2.9, [Cl^-] 78, [HCO_3^-] 24, BUN 55 mg/dL, SCr 2.7 mg/dL. Blood gas: pH 7.40, P_{CO_2} 40 mm Hg. What is/are the acid-base disturbance(s)?

Steps 1 and 2: Normal **[HCO_3^-] and** normal **pH** → "FIRST" process: not clearly detectable.

Step 3: Compensation:	$\Delta[HCO_3^-]$	ΔPCO_2
Unknown process	?	?

For the current case, there is no obvious "FIRST" process, and thus no compensation can be calculated → No calculable "SECOND" process.

Step 4: SAG = 25 → 12 normal AG + 13 anions → 13 anions must have accompanied 13 H^+. This implies the presence of a high SAG metabolic acidosis. The 13 H^+ is expected to consume 13 [HCO_3^-] → expected [HCO_3^-] = 24 − 13 = 11 ± 2, which is much lower than the actual [HCO_3^-] of 24. The higher actual [HCO_3^-] compared to the expected [HCO_3^-] suggests that the "THIRD" process is metabolic alkalosis.

Answer: High SAG metabolic acidosis and metabolic alkalosis. A possible scenario would be combined volume depletion, vomiting, and lactic acidosis with hypotension. Alternatively, this could be due to methanol intoxication and vomiting.

NOTE

- If lactic acid, ketones, and ethanol levels are negative in a patient with high suspicion for toxic ingestion who presents with elevated SAG metabolic acidosis, serum osmolality measurement is warranted to evaluate for serum osmolality gap as evidence for other ingestion.
- While a high SAG is typically associated with metabolic acidosis, a high SAG may also occur in severe metabolic alkalosis, that is, blood pH above 7.5. This is thought to be due to the conversion of previously neutral molecules to anions with severe metabolic alkalosis.

Case: A 45-year-old male with chronic obstructive pulmonary disease and heart failure with a 25% ejection fraction, who was intubated 18 hours prior due to cardiac arrest.
Blood chemistry: [Na^+] 130, [K^+] 4.6, [Cl^-] 90, [HCO_3^-] 31, BUN 45 mg/dL, SCr 3.5 mg/dL. Blood gas: pH 7.52, P_{CO_2} 39 mm Hg. Urine Cl^- 16. What is/are the acid-base disturbance(s)?
Steps 1 and 2: High **[HCO_3^-] and** high **pH** → "FIRST" process is metabolic alkalosis.

Step 3: Compensation:	$\Delta[HCO_3^-]$	ΔPCO_2
Metabolic alkalosis	↑1	↑0.7

For the current case, [HCO_3^-] ↑ by 7, P_{CO_2} thus ↑by 7 × 0.7 = 4.9 ~ 5 → expected P_{CO_2} = 40 + 5 = 45 ± 3, which is greater than the actual P_{CO_2} of 39 → there is also a respiratory alkalosis.
Step 4: SAG = 13, which is within ± 2 of normal AG of 12 → No "THIRD" process.
Answer: Metabolic alkalosis and respiratory alkalosis. Metabolic alkalosis, with urine Cl^- less than 20 mmol/L, suggests chloride-sensitive metabolic alkalosis. Posthypercapnic (ie, resolution of hypercapnia with mechanical ventilation) metabolic alkalosis is the likely diagnosis. Respiratory alkalosis is due to overventilation from the ventilator.
Case: A 32-year-old female who presents with a 3-month history of diffuse abdominal discomfort. Past medical history is notable for unprovoked left lower extremity deep venous thrombosis.
Blood chemistry: [Na^+] 138, [K^+] 4.4, [Cl^-] 96, [HCO_3^-] 17, BUN 75 mg/dL, SCr 8.2 mg/dL. Blood gas: pH 7.44, P_{CO_2} 26 mm Hg.
Steps 1 and 2: Low **[HCO_3^-] and** high **pH** → "FIRST" process is respiratory alkalosis.

Step 3: Compensation:	$\Delta[HCO_3^-]$	ΔPCO_2
Respiratory alkalosis (acute – chronic range)	↓0.1 – 0.5	↓1

For the current case, $\downarrow P_{CO_2}$ by 14, range of $\Delta[HCO_3^-]$ would be $14 \times 0.1 = 1.4 \sim 1 \pm 2$ for acute respiratory alkalosis and $14 \times 0.5 = 7 \sim 7 \pm 2$ for chronic respiratory alkalosis. The expected $[HCO_3^-]$ would thus be $(24 - 1)$ to $(24 - 7) = 17 \pm 2$ to 23 ± 2 range or 15 to 25. Since the actual $[HCO_3^-]$ is 12 and lower than the expected range of 15 to 25, there is also a metabolic acidosis → "SECOND" process is metabolic acidosis.

Step 4: SAG = 25 → 12 normal AG + 13 anions → 13 anions must have accompanied 13 H^+ → 13 H^+ is expected to consume 13 $[HCO_3^-]$ → expected $[HCO_3^-] = 24 - 13 = 11 \pm 2$, which is lower than the actual $[HCO_3^-]$ of 17 → The higher actual $[HCO_3^-]$ compared to the expected $[HCO_3^-]$ suggests that the "THIRD" process is metabolic alkalosis.

Answer: Respiratory alkalosis, high SAG metabolic acidosis, and metabolic alkalosis. This was the case of a patient with immunoglobulin G4 (IgG4)-related retroperitoneal fibrosis who presented with pulmonary embolism as a complication of lower extremity deep venous thrombosis and renal failure from obstructive uropathy. Metabolic alkalosis was likely due to hypovolemia associated with poor oral intake, which was corrected with normal saline support.

Case: A 47-year-old male who was morbidly obese with diabetes mellitus, hypertension, and sleep apnea presents with acute decompensated heart failure and severe volume overload.

Admitting arterial blood gas: pH 7.29, P_{CO_2} 55 mm Hg, P_{O_2} 70 mm Hg on 2 L of O_2. After achieving a net negative fluid balance of 8.5 L over 3 days on a bumetanide drip, the patient's oxygenation improves, but he is noted to be constantly sleepy and less conversant. Repeat blood gas: pH 7.34, P_{CO_2} 85 mm Hg. The patient continues to diurese well. Physical examination is still notable for bilateral crackles up 1/3 in both lung fields and significant peripheral edema.

Which ONE of the following is the next best step?

A. Replace fluid loss with normal saline or lactated Ringer.

B. Initiate noninvasive positive pressure support, add acetazolamide, and reduce bumetanide dose.

C. Infuse intravenous 100 mM HCl.

D. Intubate and initiate hemodialysis with ultrafiltration.

Answer: B. The rise in P_{CO_2} following large-volume diuresis is likely a compensatory response to loop diuretic-induced volume loss and metabolic alkalosis. Since the patient is still volume overloaded, more fluid needs to be removed. Since the patient still responds to diuretics, hemodialysis with ultrafiltration is not yet necessary. Acetazolamide is a diuretic that induces bicarbonaturia. This may be added transiently to correct the severe bumetanide-induced metabolic alkalosis while continuing medical diuresis.

True or false: A person walking in the street with $[HCO_3^-]$ 34 can have either a metabolic alkalosis or acute respiratory acidosis as the *only* acid-base disorder.

For acute respiratory acidosis, the compensation is $\uparrow 0.1$ HCO_3^- for every 1 increase in P_{CO_2}.

An increase in HCO_3^- of 10 (from 24) would imply an increase in P_{CO_2} of 100 mm Hg. The expected P_{CO_2} would be 100 + 40 = 140 mm Hg.

Answer: False. Although a pure metabolic alkalosis is possible, a pure acute respiratory acidosis that would give a $[HCO_3^-]$ of 34 implies that this individual would have to retain a P_{CO_2} of 140 mm Hg acutely. It is highly unlikely for an individual to have this acute rise in P_{CO_2} and still be well enough to be walking in the street.

Similarly, an individual with a $[HCO_3^-]$ of 14 is unlikely to have this value from pure acute respiratory alkalosis. A drop in $[HCO_3^-]$ of 10 would imply a drop in P_{CO_2} of 10/0.1 = 100 (for every drop of 1 in P_{CO_2}, there is a drop of 0.1 in $[HCO_3^-]$). The expected P_{CO_2} would thus be 40 − 100 = −60. This is physiologically impossible.

S2.2 Notes About SAG

Conditions with low SAG but without any associated acid-base disorder

- Hypoalbuminemia: For every drop of 1 g/dL of albumin, there is an expected drop of 2.5 in SAG. Albumin is an unmeasured anion. If albumin is low, the quantity [↓unmeasured anions$^-$ – unmeasured cations$^+$], SAG, is reduced. It is important to always correct SAG for hypoalbuminemia to unmask any high SAG acid-base disturbances.

Example: Patient with SAG of 10, serum albumin 1.5 g/dL. Assuming normal serum albumin level of 4.5 g/dL for the general population,
Corrected SAG = 10 + (4.5 − 1.5) × 2.5 = 17.5. The patient does have a ↑SAG.

- Presence of positively charged immunoglobulins: In the presence of positively charged immunoglobulins (eg, multiple myeloma, intravenous infusion of high-dose immunoglobulins), the quantity [unmeasured anions$^-$ – ↑unmeasured cations$^+$], SAG, is reduced.
- Primary hyperparathyroidism with elevated Ca^{2+} and low PO_4^{2-}: The quantity [↓unmeasured anions$^-$ – ↑unmeasured cations$^+$], SAG, is reduced. In hypercalcemic conditions with high PO_4^{2-} levels (eg, increased bone resorption), SAG [↑unmeasured anions$^-$ – ↑unmeasured cations$^+$] is likely normal.
- Falsely low measurements of S[Na^+] in the case of severe hypernatremia. When S[Na^+] is greater than 170 mmol/L, S[Na^+] measurement may not be accurate and may be falsely low.
- Falsely high measurements of Cl^- (may occur with fluoride/bromide intoxication [bromide from pyridostigmine overdose], hyperlipidemia)

An elevated SAG without associated metabolic acidosis may be seen in patients with:

- Severe metabolic alkalosis, that is, pH greater than 7.5, presumably due to the conversion of previously neutral molecules to anions in the presence of high serum bicarbonate

- Nonketotic hyperglycemia with cellular phosphate/anion extracellular leaks

APPENDIX C: Suggested Readings

CHAPTER 1: SODIUM AND WATER ABNORMALITIES

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Practice Test

1. A 32-year-old female with no known past medical history presents to the emergency department for weakness. She denies taking any medication. Physical examination reveals a thin woman, fatigue appearing, otherwise within normal limits.
   Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	138	136-145 mmol/L
Potassium	2.5	3.5-5.0 mmol/L
Chloride	122	98-106 mmol/L
Total CO_2 (bicarbonate)	6	23-28 mmol/L
Anion gap (AG)	10	10-14 mmol/L
Blood urea nitrogen (BUN)	11	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL
Estimated glomerular filtration rate (eGFR) (CKD-EPI 2021)	118	mL/min/1.73 m^2
Glucose (fasting)	98	70-100 mg/dL
Albumin	3.8	3.5-5.5 g/dL

   Arterial blood gas: pH 7.27, pCO_2 22
   Urine: Na 72 mmol/L, K 33 mmol/L, Cl 80 mmol/L, creatinine 67 mg/dL
   Urine pH: 6.0
   Which one of the following does this patient MOST likely have?

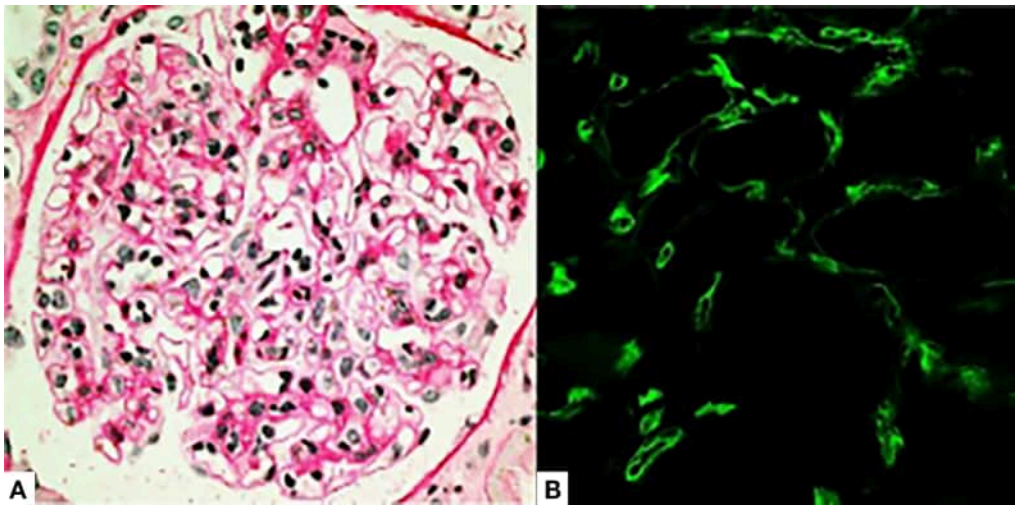
A. Distal renal tubular acidosis (RTA) type 1

B. Distal RTA type 4

C. Proximal RTA type 2

D. Diarrhea

2. A 45-year-old female with end-stage kidney disease (ESKD) secondary to biopsy-proven diabetic kidney disease received a deceased donor kidney 9 months ago. Immunologic profile at the time of transplant: class I calculated panel reactive antibody (cPRA) 5%, class II cPRA 10%; no class I or class II donor-specific antibody (DSA) was detected at the time of transplant. Pretransplant B- and T-cell complement-dependent cytotoxicity and flow cytometry crossmatch were negative. She was induced with basiliximab and high-dose intravenous (IV) methylprednisolone. She had immediate graft function and achieved a nadir serum creatinine (SCr) of 0.9 mg/dL. On a routine clinic visit, she was found to have an SCr of 2.9 mg/dL (baseline creatinine 0.9-1.1 mg/dL). Her home medications include tacrolimus 3 mg twice daily (bid), mycophenolate mofetil 1,000 mg bid, prednisone 5 mg daily, diltiazem ER 180 mg daily, carvedilol 12.5 mg bid, atorvastatin 10 mg daily, insulin glargine, and insulin aspart. She admitted to missing some of her medications on a number of occasions. On physical examination, vital signs show blood pressure (BP) 150/90 mm Hg and pulse 66 beats per minute. Her allograft site is nontender, and she has no peripheral edema. An allograft biopsy is performed (pathology shown below).



Left: periodic acid-Schiff stain, 400×. Right: C4d staining

Laboratory studies:
Creatinine 2.9 mg/dL (baseline 0.9-1.1 mg/dL)
Hemoglobin 11.2 g/dL
Hematocrit (HCT) 33.6%
Urine protein-to-creatinine ratio (uPCR) 0.2 mg/mg
Blood tacrolimus trough level 2 ng/mL (target 6-9 ng/mL)
The patient displayed de novo DSA to DQ 6 with a mean fluorescence intensity (MFI) of 11,250 and to DQ 5 with an MFI of 18,500.
DSA strength interpretation: weak MFI 1,000 to 3,000; moderate 3,000 to 8,000; strong greater than 8,000
Which ONE of the following is the MOST appropriate treatment for this patient?

A. Intravenous immunoglobulin (IVIG) alone
B. Antithymocyte globulin (ATG) alone
C. Plasmapheresis and ATG
D. Plasmapheresis and IVIG

3. Which of the following statements regarding drug removal by dialysis is CORRECT?

A. Drug clearance by dialysis is considered clinically significant if drug clearance is increased by 60% or more with dialysis.

B. In patients receiving peritoneal dialysis (PD), peritonitis may reduce drug clearance.

C. Prefilter replacement fluid (RF) in hemodiafiltration increases the proportion of drug that is removed by convection and decreases the proportion of drug that is removed by diffusion.

D. Protein-bound drugs may be better cleared with hemodialysis (HD) compared with PD.

4. Which one of the following is TRUE regarding Alport syndrome (AS)?

   A. Both male and female patients with X-linked AS carry a risk of anti-glomerular basement membrane (anti-GBM) disease after a kidney transplant.

   B. Only male patients with X-linked AS carry a risk of anti-GBM disease after a kidney transplant.

   C. Gene editing has successfully cured patients with autosomal dominant AS.

   D. AS and thin basement membrane nephropathy involve mutations in genes encoding different extracellular matrix proteins.

5. Which one of the following agents may be used in lieu of glucocorticoids (GCs) in patients with antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN)?

   A. Targeted-release formulation of budesonide

   B. Sparsentan

   C. Avacopan

   D. Methylprednisolone

6. A 55-year-old man with end stage kidney disease due to autosomal dominant polycystic kidney disease (ADPKD) underwent a living unrelated kidney transplant via paired exchange 2 years ago. He is maintained on standard triple immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone. He had excellent graft function with baseline creatinine in the 1.0 to 1.2 mg/dL range. He did well until 3 days

ago when he was started on nirmatrelvir and ritonavir combination therapy (Paxlovid) for symptomatic COVID-19 infection (runny nose, headaches, anosmia). He tolerated Paxlovid well until day 3 when he developed nausea, vomiting, and generalized muscle aches and pain. He reports poor oral intake and has only been eating chicken soup and drinking pomegranate and grapefruit juices to avoid dehydration. Basic metabolic panel shows a creatinine of 1.8 mg/dL. Tacrolimus level is 50 ng/dL (therapeutic range 5-8 ng/dL). He admits to taking St John wort for depression and anxiety because he was advised to self-isolate for 21 days. He denies over-the-counter drug use.
All of the following can lead to supratherapeutic tacrolimus level EXCEPT

A. Grapefruit juice

B. Pomegranate juice

C. St John wort

D. Paxlovid (nirmatrelvir and ritonavir combination therapy)

7. A 58-year-old male with a history of hypertension (HTN) and gout presents to your clinic to establish long-term care. Review of his presenting laboratory studies for the current visit is as follows:
Laboratory studies:

Hematology	**Patient**	**Reference range**
White blood cell (WBC) count	7.2	4-10 × 10^3/mL
Hemoglobin	12.5	Male: 14-17 g/dL
Hematocrit	37.5	Male: 45%-52%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	137	136-145 mmol/L

Hematology	Patient	Reference range
Potassium	4.2	3.5-5.0 mmol/L
Chloride	100	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	13	10-14 mmol/L
Blood urea nitrogen	48	8-20 mg/dL
Creatinine	4.0	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	17	mL/min/1.73 m^2
Glucose (fasting)	99	70-100 mg/dL
Urinalysis		
Color	dark yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.010	1.005-1.025
Glucose	Negative	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Positive	Negative
Protein	>300	Negative

Hematology	Patient	Reference range
Red blood cells (RBCs)	3-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	≤2-5 WBCs/HPF
Squamous epithelial cells	2-5	<15-20 squamous epithelial cells/HPF
Casts	None	None
Crystals	None	Occasionally

Urine studies: protein to creatinine ratio 2.1 g/g, albumin-to-creatinine ratio (ACR) 1.8 g/g

Which one of the following BEST describes his current kidney condition?

A. He has acute kidney injury (AKI).

B. He has chronic kidney disease (CKD), stage G4A3.

C. He has acute kidney disease (AKD).

D. It cannot be determined.

8. Which one of the following is the MOST accurate statement regarding HTN?

   A. Isolated systolic hypertension (ISH) occurs with stiffening of large arteries, leading to reduced vessel capacitance and acceleration of pulse wave velocity, hence widening of pulse pressure.

   B. Isolated diastolic hypertension (IDH) is more common in older females.

   C. Masked HTN is another term for white-coat hypertension (WCH).

   D. WCH is benign and does not require treatment.

9. A drug is 30% cleared by liver and 70% by kidneys. Normal maintenance dose is 100 mg. If kidney function is now 40% of normal and assuming liver clearance is preserved, what should be the new maintenance dose?

A. 48 mg

B. 58 mg

C. 70 mg

D. 62 mg

10. A 47-year-old male with a history of type 2 diabetes mellitus (T2D), diabetic kidney disease, chronic kidney disease G3bA3 (baseline eGFR ranges from 35 to 40 mL/min/1.73 m^2 over the past 6 months), HTN, and heart failure (HF) with preserved ejection fraction (HFpEF) (per echocardiogram done 2 years prior) presents with worsening pedal edema and increasing fatigue over the past 3 months. He works from home as an engineer and does not exercise. On review of systems, the patient denies any headaches, cold intolerance, chest pain, shortness of breath, abdominal pain, change in bowel movements, or urinary symptoms.

    Medications include metformin 1,000 mg bid, empagliflozin 25 mg daily, nifedipine XL 60 mg daily, losartan 50 mg daily, carvedilol 25 mg bid, furosemide 20 mg daily, and atorvastatin 80 mg daily.

    Physical examination: well-appearing male in no acute distress, alert and oriented to date, person, place, and situation

    Vital signs: weight 102 kg, body mass index 33 kg/m^2, BP 125/71 mm Hg, pulse 76 beats per minute, respiratory rate 18/min, temperature 37.2 °C

    Neck: short thick neck

    Oropharynx: within normal limits with moist oral mucosa

    Lungs: +crackles left lower lung

    Heart: normal S_1, S_2, no rubs or gallops

    Abdomen: normal bowel sounds, soft, nondistended, nontender, liver span 10 cm by percussion, no splenomegaly

    Extremities: 1 to 2+ edema up to knees bilaterally

    Deep tendon reflexes: symmetric, 2+ throughout

    Neurologic examination: nonfocal

    Laboratory studies:

Hematology	Patient	Reference range
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	12.5	Male: 14-17 g/dL
Hematocrit	37.5	Male: 45%-52%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	132	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	97	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	13	10-14 mmol/L
Blood urea nitrogen	48	8-20 mg/dL
Creatinine	4.0	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	20	mL/min/1.73 m^2
Glucose (fasting)	118	70-100 mg/dL
Urinalysis		
Color	Dark yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.010	1.005-1.025

Hematology	Patient	Reference range
Glucose	>1,000	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Positive	Negative
Protein	>600	≤150 mg/dL
Red blood cells (RBCs)	3-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	≤2-5 WBCs/HPF
Squamous epithelial cells	2-5	<15-20 squamous epithelial cells/HPF
Casts	10-15 hyaline casts	None
Crystals	None	Occasionally
Bacteria	None	None
Yeast	None	None

What is the next BEST step?

A. Add spironolactone 25 mg bid.

B. Hold furosemide.

C. Obtain two-dimensional echocardiogram.

D. Measure postvoid residual volume.

11. A 57-year-old female with a history of bilateral silicone breast implant presents with hypercalcemia. The treating physician believes that her hypercalcemia is related to granulomatous disease associated with her implants.
    Which ONE of the following sets of laboratory studies would be consistent with granulomatous disease?

	Parathyroid hormone (PTH)	$1,25(OH)_2$ vitamin D	Serum phosphorus
A.	↓	↑	Normal to ↑
B.	↑	↑	↓
C.	↓	Normal to ↑	↓
D.	↑	↓	↑

12. Which one of the following is/are the MOST accurate statement(s) regarding the use of cystatin c versus serum creatinine in the estimation of GFR?
    A. GFR formulas (CKD-EPI) using both cystatin c and SCr are generally more accurate than formulas using either cystatin c or SCr alone.
    B. GFR estimation using creatinine may over- or underestimate actual GFR based on patient characteristics such as muscle mass, whereas the use of cystatin c is unaffected by non-GFR determinants.
    C. A meta-analysis revealed that using cystatin c rather than SCr to estimate GFR led to a reclassification of 40% of patients with CKD 3a to a higher (worse) CKD stage and this was associated with a higher risk of CKD progression.
    D. Both A and C are correct.
13. A 57-year-old patient presents with the following laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	138	136-145 mmol/L
Potassium	2.5	3.5-5.0 mmol/L
Chloride	119	98-106 mmol/L
Total CO_2 (bicarbonate)	6	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	8	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	118	mL/min/1.73 m^2
Glucose (fasting)	77	70-100 mg/dL
Albumin	3.6	3.5-5.5 g/dL

Arterial blood gas: pH 7.27, pCO_2 22
Urine: Na 22 mmol/L, K 33 mmol/L, Cl 100 mmol/L
Urine pH: 6.0
Which one of the following is the BEST diagnostic test for patient's metabolic acidosis?

A. Evaluate for autoimmune disease such as Sjögren disease.

B. Evaluate for hypoaldosteronism.

C. Evaluate for Fanconi syndrome.

D. Evaluate stool for infectious etiologies and fatty content.

14. A 23-year-old female wishes to donate a kidney to her brother who has ESKD due to reflux nephropathy. She is in excellent health and has no significant past medical or surgical history. She has a body mass index of 24 kg/m^2. However, she is concerned about future pregnancy and comes to you for advice.
Which ONE of the following should she be informed about?

A. Desire to become pregnant is a contraindication to living donation.

B. Prior history of hypertensive disorders of pregnancy (eg, gestational HTN, preeclampsia, or eclampsia) is a contraindication to living donation.

C. Donation may increase the risk of preeclampsia and gestational HTN.

D. Both B and C are correct.

15. A 45-year-old female with a history of asthma, hypothyroidism, and seasonal allergies presents with poor mentation and reduced energy level. She endorses eating well at home. Her daily diet typically consists of chicken or fish, vegetables, and small portions of carbohydrates. She works as an engineer. On review of systems, patient denies any headaches, cold intolerance, chest pain, short of breath, dyspnea on exertion, abdominal pain, change in bowel movements or urinary symptoms.
Medications include albuterol metered-dose inhaler bid, levothyroxine 75 µg daily, and diphenhydramine 50 mg bid.
Physical examination: well-appearing female in no acute distress, alert and oriented to date, person, place, and situation. Patient answers all questions appropriately.
Vital signs: weight 72 kg, BP 120/73 mm Hg, pulse 76 beats per minute, respiratory rate 16/min, temperature 37.3 °C
Oropharynx: within normal limits with moist oral mucosa
Lungs, heart, abdominal examinations are within normal limits.
Extremities: no edema
Deep tendon reflexes: symmetric, 2+ throughout
Neurologic examination: nonfocal except for slow mentation
Laboratory studies:

Hematology	Patient	Reference range
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	12.5	Female: 12-16 g/dL

Hematology	Patient	Reference range
Hematocrit	37.5	Female: 37%-48%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	110	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	78	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	10	10-14 mmol/L
Blood urea nitrogen	11	8-20 mg/dL
Creatinine	0.9	0.7-1.3 mg/dL
Glucose (fasting)	78	70-100 mg/dL

Urine studies: osmolality 98 mOsm/kg, sodium less than 10 mmol/L, potassium 17 mmol/L

Which one of the following is the BEST option for the current patient's hyponatremia?

A. Refer to psychiatry.

B. Refer to an allergy medicine specialist.

C. Advise the patient to reduce water intake.

D. Refer to endocrinology.

16. You are asked to dose an antibiotic for a 100-kg anuric patient who is receiving continuous venovenous hemodiafiltration (CVVHDF) at a dose of 30 mL/kg/h. The antibiotic is known to have a free fraction of 50%.

How should the antibiotic be dosed?

A. Creatinine clearance of 25 mL/min
B. Creatinine clearance of 50 mL/min
C. Creatinine clearance of 35 mL/min
D. Creatinine clearance of less than 10 mL/min

17. Which one of the following drugs is NOT dialyzable?
    A. Metformin
    B. Dabigatran
    C. Metoprolol
    D. Carvedilol
18. A 60-year-old female with a history of HTN, type 2 diabetes mellitus (T2D), and rheumatoid arthritis presents with severe headaches and is found to have a subarachnoid hemorrhage. You are consulted for newly developed hyponatremia. Review of systems is notable for generalized headaches.
    Chart review reveals the following:
    Day 1: serum sodium 140 mmol/L, potassium 4.4 mmol/L
    Input: lactated Ringer at 75 mL/h (1.8 L/d), 500 mL of water mixed with medications; output 1.8 L
    Day 2: serum sodium 137 mmol/L, potassium 4.3 mmol/L
    Input: lactated Ringer at 75 mL/h (1.8 L/d); output 2.4 L
    Urine studies: sodium 147 mmol/L, potassium 25 mmol/L
    Day 3: serum sodium 132 mmol/L, potassium 4.0 mmol/L, uric acid 3.2 mg/dL
    Input: lactated Ringer at 75 mL/h (1.8 L/d); output 2.2 L
    Urine studies: sodium 117 mmol/L, potassium 25 mmol/L, osmolality 398 mOsm/kg
    Day 4: sodium 129 mmol/L
    Morning cortisol 21 (normal 5-25 microg/dL)
    Thyroid-stimulating hormone 2.4 mIU/L (normal 0.4-4.0 mIU/L)
    Physical examination: Patient appears fatigued but is alert and oriented to date, person, place, and situation.
    Vital signs: weight 87 kg, BP 140/63 mm Hg, pulse 98 beats per minute, respiratory rate 19/min, temperature 37.6 °C
    Oropharynx: dry oral mucosa

Lungs, heart, abdominal examinations are within normal limits.
Extremities: no edema
Which one of the following is the MOST likely diagnosis?

A. Syndrome of inappropriate antidiuretic hormone release (SIADH)
B. Complete central diabetes insipidus (DI)
C. Adrenal insufficiency
D. Cerebral salt wasting (CSW)

19. Which one of the following statements is TRUE regarding focal segmental glomerulosclerosis (FSGS)?

A. Adult patients with FSGS secondary to a genetic mutation should be treated with immunosuppression if they have nephrotic range proteinuria.
B. Pending approval of specific apolipoprotein L1 (APOL1) medications, patients with two APOL1 risk variants and FSGS with nephrotic syndrome (NS) should receive the same treatment as patients with FSGS without APOL1 risk variants.
C. Hematuria is a risk factor for progression of end stage kidney disease in patients with FSGS.
D. Antinephrin antibodies are only associated with FSGS in some children, but not in adults.

20. Drugs with metabolites that accumulate in patients with reduced kidney function leading to significant adverse effects include all the following EXCEPT:

A. Allopurinol
B. Dolutegravir
C. Venlafaxine
D. Morphine
E. Nitroprusside

21. Which one of the following is the MOST common form of kidney disease seen *currently* in patients with human immunodeficiency virus (HIV)?

A. HIV immune complex–associated kidney disease (HIVICK)
B. Tenofovir-associated kidney disease
C. Diabetic nephropathy
D. HIV-associated nephropathy (HIVAN)

22. Which one of the following statements is TRUE regarding sodium glucose cotransporter 2 inhibitors (SGLT2i)?
    A. SGLT2i-induced acute dip in eGFR is due primarily to efferent vasodilatation similar to angiotensin converting enzyme inhibitors and angiotensin receptor blockers.
    B. The 2022 ADA-KDIGO guidelines recommend discontinuing SGLT2i when eGFR falls below 20 mL/min.
    C. The renoprotective effect of SGLT2i depends on adequate kidney function (eGFR >30-45 mL/min).
    D. SGLT2i reduces the rate of kidney disease progression in patients with chronic kidney disease, independent of their glucose-lowering effect.
23. A 57-year-old woman with limited-stage small cell cancer of the lung was admitted for cisplatin (80 mg/m^2) and etoposide (100 mg/m^2) therapy. Medications: omeprazole, azithromycin, acetaminophen, normal saline infusion at 75 mL/h. You are asked to see the patient for a rapid decrease in serum sodium from 138 to 133 and 125 mmol/L within 24 and 48 hours of chemotherapy, respectively. A diagnosis of syndrome of inappropriate release of antidiuretic hormone (SIADH) was initially made. Despite free water restriction, her serum sodium concentration continued to decrease in association with the acute onset of headaches, nausea, and dizziness.
    Physical examination: ill appearing
    Vital signs: weight 68 kg, BP 105/51 mm Hg, pulse 86/min, respiratory rate 16/min, temperature 37.2 °C
    Oropharynx: dry oral mucosa
    Lungs: minimal crackles left lower lung
    Heart: normal S_1, S_2, no rubs or gallops

Abdomen: normal bowel sounds, soft, nondistended, nontender, no hepatomegaly
Extremities: no edema
Neurologic examination: nonfocal
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	125	136-145 mmol/L
Potassium	3.7	3.5-5.0 mmol/L
Chloride	93	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	10	10-14 mmol/L
Blood urea nitrogen	21	8-20 mg/dL
Creatinine	0.9	0.7-1.3 mg/dL
Glucose (fasting)	100	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	2.9	3-4.5 mg/dL
Magnesium	1.7	1.5-2.4 mg/dL
Urinalysis	**Patient**	**Normal range**
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.022	1.005-1.025
Glucose	100 mg/dL	Negative
Ketones	Positive	Negative

Serum chemistry	Patient	Normal range
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Negative	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	0-1	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	≤2-5 WBCs/HPF
Squamous epithelial cells	2-5	<15-20 squamous epithelial cells/HPF
Casts	5-10 hyaline casts	None

Which one of the following is the MOST likely diagnosis?

A. Acute interstitial nephritis (AIN) from proton pump inhibitor
B. Malignant pericardial effusion
C. Fanconi syndrome with renal salt wasting from cisplatin
D. Adrenal insufficiency

24. Which one of the following equations BEST estimates the glomerular filtration rate of a 45-year-old male with a body mass index of 42 kg/m^2?

A. Creatinine-based CKD-EPI 2021 equation
B. Combined creatinine and cystatin-based CKD-EPI 2021 equation
C. Cystatin-based CKD-EPI 2021 equation
D. Cockcroft-Gault (CG) formula

25. A 24-year-old man presents with nephrotic syndrom. He also reports that he has been developing cherry-red "spots" on his pelvic skin. He rarely sweats, even after prolonged exercise. Review of systems is notable for intermittent pain shooting down his legs. Family history is notable for his mother who developed mild proteinuria and similar but milder symptoms at the later onset in life.
    Which of the following is MOST likely to be found on this patient's kidney biopsy?
    A. Thrombotic microangiopathy (TMA)
    B. Glomerular basement membrane scalloping
    C. Lysosomal inclusion bodies (aka Zebra bodies) mostly in podocytes, containing globotriaosylceramide (Gb3)
    D. Glomerular basement membrane thinning
26. Cystatin-based equation for estimating GFR may be used for which ONE of the following conditions if it would impact treatment decisions?
    A. Malnutrition
    B. Eating disorder without other comorbidities (eg, anorexia)
    C. Advanced cancer
    D. Anabolic steroid use
27. In addition to dietary sodium restriction, significant volume overload in patients with CKD is BEST treated with which one of the following?
    A. Loop diuretic
    B. Sodium glucose cotransporter 2 inhibitor (SGLT2i) and a loop diuretic
    C. SGLT2i
    D. Thiazide diuretic
28. A 54-year-old Caucasian male recently diagnosed with IgA nephropathy with current clinical findings below presents for a

second opinion regarding his prognosis. Medication: sparsentan × 4 months
Allergies: angioedema with angiotensin converting enzyme inhibitosr
SCr 1.5 mg/dL
Urine protein 1.2 g/d (1.5 g/d 3 months prior)
Urinalysis with 10 to 15 red blood cells per high powerfield (RBCs/HPF)
Kidney biopsy MEST-C classification of IgAN done 4 months prior
Mesangial hypercellularity M1 (M0-M1)
Endocapillary hypercellularity E1 (E0-E1)
Segmental sclerosis or adhesion S1 (S0-S1)
Tubular atrophy and interstitial fibrosis T0 (T0-T2)
Crescents C0 (C0-C2)
Which one of the following options BEST outlines factors associated with high-risk disease and potential worse outcome?

A.	–	–	10-15 RBCs/HPF	MEST-C score
B.	Serum creatinine 1.5 mg/dL	Urine protein 1.2 g/d	10-15 RBCs/HPF	MEST-C score
C.	Serum creatinine 1.5 mg/dL	Urine protein 1.2 g/d	10-15 RBCs/HPF	–
D.	–	Urine protein 1.2 g/d	–	MEST-C score

29. A 58-year-old male with a history of IgA nephropathy, diagnosed 5 years ago and in remission for the past 5 years, hyperlipidemia, and hypertension presents for routine follow-up. His current medications include omeprazole, acetaminophen as needed for headaches, and losartan. Physical examination is unremarkable. BP is 120/70 mm Hg.
Laboratory studies are notable for a decline in creatinine-based eGFR from 67 (4 months prior) to 52 mL/min/1.73 m^2.
Which one of the following is the next BEST step?

A. The GFR decline is expected given patient's multiple comorbidities.

B. Evaluate for a reversible cause for patient's glomerular filtration rate decline.

C. Administer intravenous glucocorticoid pulse.

D. The observed GFR change is likely within the margin of error for measuring SCr.

30. A 72-year-old male with a history of granulomatous polyangiitis associated with anti-myeloperoxidase (MPO) antibody, diagnosed 6 months ago, presents for routine follow-up. He was induced with rituximab (RTX) and continued on the same medication for maintenance.

    At the current visit, his anti-MPO antibody level is noted to be 7 IU/mL (previously negative) (MPO 3.5-5.0 IU/mL is considered equivocal and >5.0 IU/mL is positive). Serum creatinine (SCr) is at baseline of 1.4 mg/dL. Urinalysis is bland without cells or casts. Urine protein to creatinine ratio is 0.4 g/g creatinine (0.5 g/g 1 month prior).

    Current medications: irbesartan, RTX at 6-month intervals

    Which one of the following is the next BEST step?

    A. Monitor clinical markers (urinalysis, SCr, anti-MPO titer more closely).

    B. Pulse with methylprednisolone.

    C. Initiate oral prednisone.

    D. Administer an extra dose of RTX.

31. A 66-year-old man has ESKD due to biopsy-proven diabetic kidney disease. He was started on hemodialysis 3 months ago for volume overload refractory to diuretics. He came to you for kidney transplant evaluation. The patient is O blood type. He currently has no potential living donor, and the current average waiting time for a deceased donor kidney for O blood type is from 8 to 10 years. He was informed that consenting for deceased donor kidneys with a kidney donor profile index (KDPI) of 0% to 85% as well as those with KDPI more than 85% may increase his chance

of receiving a kidney transplant sooner compared with consenting for kidneys with KDPI of 0% to 85% alone. The patient asked for your advice about consenting for a deceased donor kidney with a KDPI of more than 85%.
Which ONE of the following is correct?

A. This patient should only accept deceased donor kidney with KDPI of 0% to 85% because he is diabetic.
B. Deceased donor kidney with a KDPI of more than 85% is associated with an increased risk of hepatitis C virus (HCV) infection.
C. The 10 donor characteristics used to calculate KDPI include gender, age, weight, ethnicity, history of HTN, history of diabetes, SCr, cause of death, hepatitis C status, and donation after circulatory death status.
D. Lower KDPI values are associated with longer estimated function.

32. A 57-year-old male with a history of T2D and CKD stage G3bA3 presents for follow-up 4 weeks after the initiation of dapagliflozin. He feels well and denies any urinary symptoms.
His eGFR is noted to decrease from a baseline of 45 to 30 mL/min/1.73 m^2. Urinalysis is bland.
Which one of the following is the next BEST step?

A. Prepare for kidney replacement therapy.
B. Discontinue dapagliflozin.
C. Hold dapagliflozin and investigate the cause of eGFR decline.
D. Continue dapagliflozin and monitor closely in case of a continuing decline in eGFR.

33. A 45-year-old female with type 2 diabetes mellitus and hypertension presents to the emergency department for severe abdominal pain. The patient denies fevers, chills, change in bowel movement, difficulty voiding, any recent traveling, or ingestion of raw seafood. She mentions that she started on the low-carbohydrate Atkins diet this past week for weight loss.

Medications: irbesartan, empagliflozin, amlodipine
Physical examination
Vital signs: weight 102 kg, height 1.75 m, body mass index 33 kg/m^2, BP 155/90 mm Hg, pulse 86 beats per minute, respiratory rate 20/min, temperature 37.2 °C
Oropharynx: within normal limits with moist oral mucosa
Lungs: clear to auscultation bilaterally
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: obese, normal bowel sounds, diffusely tender with palpation, no hepatosplenomegaly
Extremities: trace ankle edema bilaterally
Neurologic examination: nonfocal
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	133	136-145 mmol/L
Potassium	4.6	3.5-5.0 mmol/L
Chloride	100	98-106 mmol/L
Total CO_2 (bicarbonate)	15	23-28 mmol/L
Anion gap	18	10-14 mmol/L
Blood urea nitrogen	22	8-20 mg/dL
Creatinine	1.2	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	57	mL/min/1.73 m^2
Glucose (fasting)	175	70-100 mg/dL
Albumin	3.9	3.5-5.5 g/dL

Which one of the following is the next BEST step?

A. Obtain urine sodium, potassium, and chloride or urine ammonium level.

B. Obtain serum ketones and blood gas.

C. Obtain kidney ultrasound and bladder scan to evaluate for urinary obstruction.

D. Obtain liver function tests and lipase.

34. A 25-year-old athletic and muscular female with a history of minimal change disease (MCD) presents for routine follow-up with her nephrologist when she is also found to have a urinary tract infection.
Medications: furosemide 20 mg daily, protein supplement
Urine albumin to creatinine ratio 1.6 g/g creatinine
Which one of the following can give rise to a FALSELY high urine albumin to creatinine ratio in this patient?

A. Muscular built stature

B. Furosemide

C. Urinary tract infection

D. High protein intake

35. Which one of the following is a CORRECT statement regarding the management of pregnant patients with lupus nephritis (LN)?

A. Hydroxychloroquine maintenance therapy should be discontinued during pregnancy.

B. Start low-dose aspirin 100 mg/d or less after gestational age of 16 weeks to reduce the risk of preeclampsia, intrauterine growth retardation, and fetal loss.

C. LN relapse during pregnancy should be treated with glucocorticoid, and if necessary, azathioprine (AZA).

D. The use of mycophenolic acid (MPA) is safe during pregnancy.

36. A 56-year-old male with a history of gout, renal salt wasting, and chronic kidney disease of unknown etiology is admitted for increased joint pain in his hands and end stage kidney disease. His family history is notable for a history of hyperuricemia and gout in his paternal grandmother, aunt, first cousin, and father. His aunt and now-deceased grandmother had required kidney replacement therapy.

The patient's laboratory studies are notable for an eGFR 7 mL/min/1.73 m^2, hemoglobin 11 g/dL, and serum uric acid 12.9 mg/dL (reference range 2.6-6.0 mg/dL). Fractional uric acid excretion is reduced at 3.5%.

Kidney ultrasound reveals bilateral atrophic kidneys with thinned cortices.

Which one of the following is the MOST likely diagnosis?

A. Autosomal dominant tubulointerstitial kidney disease associated with mutation of the hepatocyte nuclear factor-1β (ADTKD-HNF1β)

B. Autosomal recessive tubulointerstitial disease (aka nephronophthisis or NPHP)

C. Tuberous sclerosis syndrome

D. ADTKD associated with UMOD mutation (ADTKD-UMOD)

37. An 18-year-old male with advanced chronic kidney disease due to ADTKD-HNF1β and diabetes mellitus refuses to take his sodium bicarbonate supplement for his metabolic acidosis.

Which ONE of the following is/are associated with chronic metabolic acidosis?

A. Reduced thyroid function

B. Short stature with reduced muscle mass

C. Increased need for insulin

D. All of the above

38. A 50-year-old male with no known medical history presents with a 2-week history of abdominal discomfort, anorexia, and dry coughs. He works from home as an accountant. On review of systems, the patient denies any headaches, cold intolerance, chest pain, short of breath, abdominal pain, change in bowel movements, or urinary symptoms. His serum creatinine was reported to be 1.2 mg/dL 1 month prior to the current presentation.

Medications: acetaminophen 650 mg bid × 7 days

Social history: drinks up to six-pack of beer with friends on weekends
Physical examination: thin-appearing male, ill appearing, alert and oriented to date, person, place, and situation
Vital signs: weight 82 kg, body mass index 24.5 kg/m^2, BP 122/64 mm Hg, pulse 86 beats per minute, respiratory rate 18/min, temperature 37.5 °C
Neck: flat neck vein, no lymphadenopathy
Oropharynx: dry oral mucosa
Lungs: few crackles left lower lobe
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: protuberant, normal bowel sounds, soft, no hepatomegaly, nontender
Extremities: no edema
Deep tendon reflexes: symmetric, 2+ throughout
Neurologic examination: nonfocal
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	6.2	4-10 × 10^3/mL
Hemoglobin	13.5	Male: 14-17 g/dL
Hematocrit	40.5	Male: 45%-52%
Platelet count	208	150-350 × 10^3/mL
Mean corpuscular volume	82	80-100 fL
Serum chemistry		
Sodium	132	136-145 mmol/L
Potassium	5.1	3.5-5.0 mmol/L
Chloride	95	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L

Hematology	Patient	Reference range
Anion gap	16	10-14 mmol/L
Blood urea nitrogen	68	8-20 mg/dL
Creatinine	3.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	32	mL/min/1.73 m^2
Glucose (fasting)	78	70-100 mg/dL
Urinalysis		
Color	Brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.011	1.005-1.025
Glucose	>1,000	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Positive	Negative
Protein	>600	≤150 mg/dL
Red blood cells (RBCs)	10-20 dysmorphic	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	2-5	≤2-5 WBCs/HPF

Hematology	Patient	Reference range
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	Granular casts	None
Crystals	None	Occasionally
Bacteria	None	None
Yeast	None	None

Urine protein to creatinine ration 1.5 g/g
Urine albumin to creatinine ratio 1.2 g/g
Kidney ultrasound: right kidney 12 cm, left kidney 11.8 cm, normal corticomedullary differentiation, no hydronephrosis, cyst, or mass
What is the next BEST diagnostic step for this patient's current condition?

A. Infuse 25% albumin at 1 g/kg/d in divided doses.

B. Perform a kidney biopsy.

C. Obtain liver function tests.

D. Obtain a urology consult.

39. A 42-year-old male patient with a history of schizophrenia, psychogenic polydipsia, and alcohol-associated cirrhosis with moderate ascites is admitted with the following laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	113	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	80	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L

Serum chemistry	Patient	Reference range
Anion gap	11	10-14 mmol/L
Blood urea nitrogen	9	8-20 mg/dL
Creatinine	1.4	0.7-1.3 mg/dL
Glucose (fasting)	89	70-100 mg/dL

Urine studies: osmolality 125 mOsm/kg, sodium 21 mmol/L, potassium 19 mmol/L

In addition to restricting free water intake, which one of the following may be the BEST option in safely improving this patient's hyponatremia?

A. Add tolvaptan.

B. Add salt tablets.

C. Add lithium.

D. Increase solute intake.

40. A 67-year-old female with end stage kidney disease, hemodialysis (HD) dependent, type 2 diabetes mellitus, hypertension and recently diagnosed with presumed calcific uremic arteriolopathy presents with altered mental status and hypotension. Her last dialysis was the day prior to admission. Her monthly dialysis K_t/V obtained 1 week prior was 1.4.

Medications: vancomycin, carvedilol, lisinopril, sodium thiosulfate (STS) (given with HD)

Evaluation from the emergency department reveals a primary increased serum anion gap (SAG) metabolic acidosis and metabolic alkalosis (pH 7.30, pCO_2 33, bicarbonate 15 mmol/L, SAG of 32 mmol/L). Lactate and β-hydroxybutyrate are not elevated. Three sets of blood cultures and full-body helical computed tomography (CT) are negative. Physical examination is notable for several ulcerated lesions with eschar on her pannus. Vital signs are within acceptable range and without fevers.

What is the MOST likely cause of her presentation?

A. Vancomycin toxicity
B. Sodium thiosulfate
C. Inadequate dialysis
D. Sepsis

41. Which one of the following statements is CORRECT regarding antifungal agents?
    A. Fluconazole is metabolized by the liver and does not require dose reduction in patients with advanced chronic kidney disease.
    B. All azole antifungals are dialyzable and should be dosed after dialysis.
    C. Similar to the azole antifungals, the echinocandins (such as micafungin and anidulafungin) can significantly increase blood levels of calcineurin inhibitors (CNIs).
    D. The echinocandins do not require dose adjustment in patients with renal impairment including those receiving HD or continuous kidney replacement therapy (CKRT).
42. A 32-year-old female weighing 70 kg presents with normal kidney function and hypercalcemia and is found the have the following:

Endocrine	**Patient**	**Reference range**
Parathyroid hormone	124	10-65 pg/mL
Vitamin D: 1,25-dihydroxy	78	25-65 pg/mL
Calcium	11.2	9-10.5 mg/dL
Phosphorus	2.5	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL
Albumin	4.1	3.5-5.5 g/dL
24-h urine study		
Creatinine	1,300	Women: 15-20 mg/kg

Endocrine	Patient	Reference range
		Men: 20-25 mg/kg
Volume	2,800	Variable
pH	5.5	Variable
Calcium	22	Women: <200 mg/24 h; Men: <250 mg/24 h

Which one of the following is the next BEST step?

A. Obtain a surgical consult for parathyroidectomy.

B. Give a trial of burosumab (anti-fibroblast growth factor 23 [FGF-23] antibody).

C. Unable to assess due to overcollection of 24-hour urine.

D. Give a trial of calcimimetic.

43. A 51-year-old female with cirrhosis from autoimmune hepatitis is referred to the emergency department by her primary care provider for evaluation of an acute rise in serum creatinine (0.8 mg/dL 2 weeks ago, now 3.9 mg/dL). The patient denies any acute illness, traveling, change in diet, vomiting, diarrhea, change in medications, or use of nonsteroidal anti-inflammatory drugs (NSAIDs).
Prescribed medications: prednisone 5 mg daily, spironolactone 25 mg bid, furosemide 20 mg daily. The patient admitted that she did not take any of her medications this past week due to depression.
Physical examination: thin-appearing female, jaundice, alert and oriented to date, person, place, and situation
Vital signs: weight 70 kg, body mass index 26.7 kg/m^2, BP 98/60 mm Hg, pulse 87 beats per minute, respiratory rate 17/min, temperature 37.1 °C
Neck: no distended neck vein, no lymphadenopathy
Oropharynx: moist oral mucosa

Lungs: few bibasilar crackles
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: distended, normal bowel sounds, tense, nontender, +fluid shift
Extremities: 2+ edema up to knees bilaterally
Skin: jaundice, no rash
Deep tendon reflexes: symmetric, 2+ throughout
Neurologic examination: nonfocal
Laboratory studies:

Serum chemistry	**Patient**	**Reference range**
Sodium	132	136-145 mmol/L
Potassium	3.8	3.5-5.0 mmol/L
Chloride	100	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	10	10-14 mmol/L
Blood urea nitrogen	59	8-20 mg/dL
Creatinine	3.9	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	19	mL/min/1.73 m^2
Glucose (fasting)	81	70-100 mg/dL
Liver function tests		
Total protein	5.4	6.0-7.8 g/dL
Albumin	2.5	3.5-5.5 g/dL
Alanine aminotransferase (ALT)	378	0-35 U/L
Aspartate aminotransferase (AST)	427	0-35 U/L

Serum chemistry	Patient	Reference range
Alkaline phosphatase	100	36-92 U/L
Total bilirubin	11.7	0.3-1.2 mg/dL
Direct bilirubin	5.7	0-0.3 mg/dL
Urinalysis		
Color	Dark brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.009	1.005-1.025
Glucose	None	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Positive	Negative
Bilirubin	Positive	Negative
Urobilirubin	3.0	0.5-1.0 mg/dL
Blood	Positive	Negative
Protein	300	≤150 mg/dL
Red blood cells (RBCs)	>50	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	5-10	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	Few granular casts	None

Serum chemistry	Patient	Reference range
Crystals	None	Occasionally
Bacteria	None	None

Urine protein to creatinine ratio 1.1 g/g
Kidney ultrasound: right kidney 9.3 cm, left kidney 9.6 cm, normal corticomedullary differentiation, no hydronephrosis, cyst, or mass
Which ONE of the following would exclude the diagnosis of hepatorenal syndrome (HRS) and needs further evaluation at this time?

A. Medication nonadherence
B. Total bilirubin greater than 10 mg/dL
C. Hypotension
D. Proteinuria greater than 500 mg/d and hematuria with greater than 50 red blood cells per high powerfield

44. All of the following drug combination therapies can cause significant drug-drug interaction EXCEPT:

A. Nirmatrelvir-ritonavir (Paxlovid) and calcineurin inhibitors
B. Cyclosporine and statins
C. Tacrolimus and statins
D. Azathioprine and allopurinol

45. Which ONE of the following histopathologic findings can differentiate membranous nephropathy (MN) associated with lupus nephritis (LN) (class V LN) from primary MN?

A. Predominant deposition of IgG on immunofluorescence microscopy in class V LN, but not in primary MN
B. Immunofluorescence staining for IgG (strong), IgA, IgM, C1q (strong), and C3 in class V LN, but not in primary MN
C. Presence of much more severe podocytopathy in class V LN compared with primary MN

D. Presence of cytoplasmic tubuloreticular inclusions in endothelial cells in primary MN, but not in class V LN

46. A 42-year-old homeless male is brought to the emergency department after being found down by the police. No medical history can be obtained.
Physical examination
General: lethargic, intermittent vomiting without blood or coffee-ground materials, sweet fruity breath odor
Vital signs: weight 72 kg, body mass index 19 kg/m^2, BP 98/54 mm Hg, pulse 96 beats per minute, respiratory rate 18/min, temperature 37.2 °C
Oropharynx: dry oral mucosa, poor dentition
Lungs: clear to auscultation bilaterally
Heart: hyperdynamic, no rubs or gallops
Abdomen: thin, normal bowel sounds, mild midepigastric tenderness, no hepatosplenomegaly
Extremities: no edema
Neurologic examination: nonfocal
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	12.5	Male: 14-17 g/dL
Hematocrit	37.5	Male: 45%-52%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	98	80-100 fL
Serum chemistry		
Sodium	130	136-145 mmol/L
Potassium	3.8	3.5-5.0 mmol/L
Chloride	90	98-106 mmol/L

Hematology	Patient	Reference range
Total CO_2 (bicarbonate)	6	23-28 mmol/L
Anion gap	34	10-14 mmol/L
Blood urea nitrogen	48	8-20 mg/dL
Creatinine	1.4	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	48	mL/min/1.73 m^2
Glucose (fasting)	79	70-100 mg/dL
Lactic acid	11.0	0.67-1.8 mmol/L
β-Hydroxybutyrate	6.7	<0.5 mmol/L
Acetoacetic acid	1.0	<0.7 mmol/L

Venous blood gas: pH 7.10, pCO_2 20 mm Hg

What is the MOST likely diagnosis?

A. Diabetic ketoacidosis (DKA)

B. Alcohol ketoacidosis (AKA)

C. Starvation ketoacidosis (SKA)

D. Pyroglutamic acid (PA) accumulation

47. A 56-year-old female with no known medical history presents with total body pain for the past 4 weeks. Medications: acetaminophen 650 mg bid to 3 times a day (tid) as needed for pain over the past 2 weeks.

Laboratory studies:

Hematology	Patient	Reference range
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	8.5	Female: 12-16 g/dL
Hematocrit	25.3	Female: 37%-48%

Hematology	Patient	Reference range
Platelet count	204	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	130	136-145 mmol/L
Potassium	4.8	3.5-5.0 mmol/L
Chloride	111	98-106 mmol/L
Total CO_2 (bicarbonate)	12	23-28 mmol/L
Anion gap	7	10-14 mmol/L
Blood urea nitrogen	78	8-20 mg/dL
Creatinine	5.6	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	8	mL/min/1.73 m^2
Glucose (fasting)	79	70-100 mg/dL
Lactic acid	1.2	0.67-1.8 mmol/L
Albumin	3.6	3.5-5.5 g/dL
Urinalysis		
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.025	1.005-1.025
Glucose	200	<130 mg/dL
Ketones	Positive	None

Hematology	Patient	Reference range
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Negative	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	0-5	<2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	<2-5 WBCs/HPF
Squamous epithelial cells	2-5	<15-20 squamous epithelial cells/HPF

Urine protein to creatinine ratio 3.4 g/g
Venous blood gas: pH 7.3, pCO_2 26 mm Hg
What is the next BEST step?

A. Evaluate for renal tubular acidosis.
B. Check acetaminophen level.
C. Evaluate for retroperitoneal fibrosis.
D. Evaluate for paraproteinemia.

48. Which ONE of the following electrolyte disturbances may contribute to persistent metabolic alkalosis?

A. Hypokalemia
B. Hypocalcemia
C. Hypermagnesemia
D. Hyperkalemia

49. Which ONE of the following is CORRECT regarding vaccinations in the post-transplantation period?

A. Live vaccinations are generally safe and effective if given after the first 3 months post-transplantation.

B. Assessing measles antibody to determine the need for revaccination after transplantation is recommended.

C. Vaccinations during the first 3 months after transplantation may result in acute rejection and should be avoided.

D. Vaccinations should be administered at least 4 weeks before transplant.

50. A 35-year-old male presents for a routine clinic visit with the following laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	142	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	99	98-106 mmol/L
Total CO_2 (bicarbonate)	32	23-28 mmol/L
Anion gap	11	10-14 mmol/L
Blood urea nitrogen	15	8-20 mg/dL
Creatinine	1.2	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	8	mL/min/1.73 m^2
Glucose (fasting)	99	70-100 mg/dL
Albumin	4.5	3.5-5.5 g/dL

Arterial blood gas: pH 7.47, pCO_2 46 mm Hg

Urine sodium: 67 mmol/L, urine chloride 32 mmol/L

Which ONE of the following diagnoses could be consistent with this patient's laboratory studies?

A. Acute vomiting

B. Milk-alkali syndrome

C. Posthypercapnia

D. Chronic vomiting

51. Consider the human leukocyte antigen (HLA) *phenotypes* of the following two unrelated donor-recipient pair:
    Donor: A 1,2; B 8,37; DR 4,17; DQ 2,9
    Recipient: A 1,25; B 8,50; DR 4,11; DQ 2,6
    Which ONE(s) of the following statements is (are) correct?
    A. The recipient is a one haplotype match with the donor.
    B. The recipient is a one haplotype mismatch with the donor.
    C. The recipient is a four HLA-A, HLA-B, HLA-DR, HLA-DQ match with the donor.
    D. All of the above are correct.
52. Infusion of hyperoncotic albumin (ie, 25% albumin) is not beneficial and may even be harmful for which ONE of the following patients with cirrhosis and ascites?
    A. Patient presenting with anasarca and acute kidney injury (AKI)
    B. Patient presenting with spontaneous bacterial peritonitis
    C. Patient presenting with HRS requiring vasopressor support and peripheral edema
    D. Patient presenting with AKI, and dry wrinkled skin throughout
53. A 67-year-old female with a history of diabetes mellitus and chronic kidney disease is admitted to the hospital with new-onset abdominal pain, hypotension, high fevers, and leukocytosis. Blood cultures are positive for *Escherichia coli*. An abdominal CT scan with intravenous contrast reveals diverticulitis and colonic perforation. She is taken urgently to the operating room for extensive bowel resection. After the operation, she is admitted to the intensive care unit (ICU). She is intubated and sedated, and hypotensive, on two vasoactive agents. Laboratory studies reveal serum creatinine (SCr) 4.8 mg/dL, potassium 6.4 mmol/L, total CO2 17 mmol/L, and arterial blood pH 7.15. Nephrology is consulted for oliguric acute kidney injury. Continuous kidney replacement therapy using a glucose-free, phosphorus-containing, bicarbonate dialysate is initiated. Routine chemistry on day 3 reveals SCr 1.5 mg/dL, potassium 4.1 mg/dL, CO2 17 mmol/L,

and anion gap of 22 mmol/L. Arterial blood gas reveals pH 7.33 and pCO2 33 mm Hg. With the exception of vasopressors and broad spectrum antibiotics, no other medication is given.
Which one of the following is the MOST likely explanation for the elevated anion gap metabolic acidosis?

A. D-Lactic acidosis

B. Ketoacidosis

C. Pyroglutamic acidosis

D. Kidney failure with inadequate dosing of CKRT

54. Which ONE of the following conditions may present with histopathologic features of C3 glomerulopathy (C3G) and, therefore, must be ruled out as clinically indicated when a biopsy diagnosis of C3G is given?

A. Paraproteinemia

B. Postinfectious GN

C. Mutations/genetic variants of complement regulators

D. All of the above

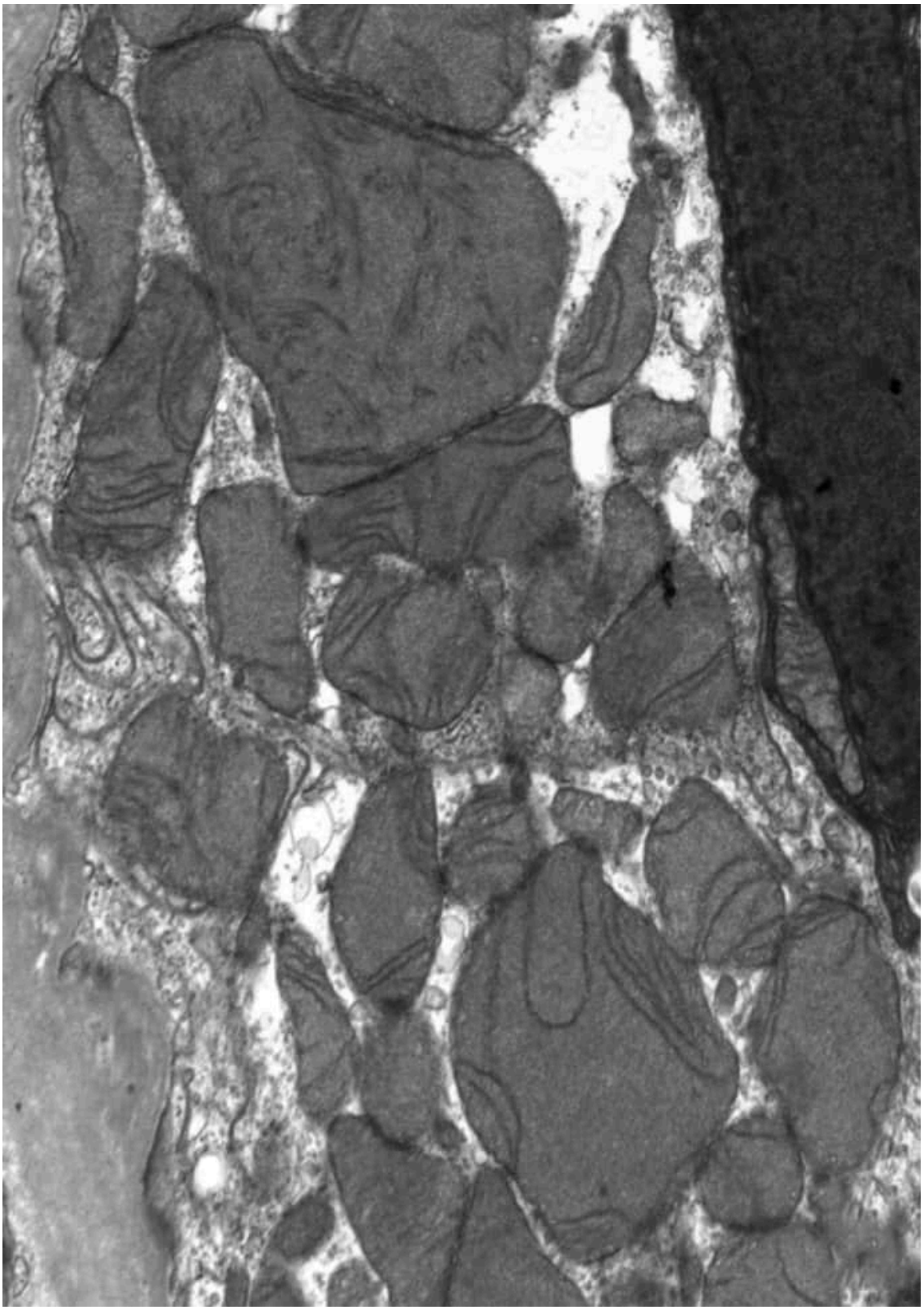
55. Which ONE of the following medications may present with proximal tubular mitochondrial injury as shown?

A. Acyclovir

B. Tenofovir

C. Gentamicin

D. Ascorbic acid



56. Which one of the following is the BEST treatment for a patient with 2,8-dihydroxyadenine (2,8-DHA)-associated crystalline

nephropathy?

A. Sodium restriction and forced diuresis
B. Dietary calcium restriction
C. Urine alkalinization with sodium bicarbonate
D. Allopurinol and low-purine diet

57. Immunologic risk assessment of the potential kidney transplant recipient at the time of organ offer includes all of the following EXCEPT:

A. **Calculated panel reactive antibody (cPRA)**
B. Presence of anti-HLA donor specific antibodies
C. Kidney donor profile index (KDPI)
D. Degree of HLA mismatching

58. A 72-year-old male with a history of diabetes mellitus, hyperlipidemia, hypocalcemia due to vitamin D deficiency, and chronic kidney disease stage G3aA1 presents to the emergency department for angina. Physical examination suggests euvolemia. The cardiology team recommends cardiac catheterization with potential intervention.
Which one of the following is the BEST preventive therapy for contrast-associated acute kidney injury (AKI)?

A. Infusion of sodium bicarbonate pre- and postcontrast study
B. Infusion of normal saline pre- and postcontrast study
C. Remote ischemic preconditioning
D. Infusion of normal saline pre- and postcontrast study and use of *N*-acetylcysteine

59. A 52-year-old female with ESKD secondary to lupus nephritis received a deceased donor kidney transplant 2 weeks ago. Immunologic profile at the time of transplant: class I cPRA 50%, class II cPRA 70%. No class I or class II DSA was detected. She was induced with antithymocyte globulin due to high immunologic risk. Her maintenance immunosuppression consists of tacrolimus, mycophenolate mofetil, and prednisone. She had immediate graft

function and was discharged home on postoperative day 4 (POD 4) with Jackson-Pratt (JP) drain in place. Serum creatinine (SCr) at the time of discharge was 2.1 mg/dL (pretransplant SCr was 10 mg/dL). She was seen in the clinic on POD 7. Routine laboratory studies done on the day of her visit showed a creatinine of 1.6 mg/dL. Overall, she reported doing well, except for mild incisional pain relieved with acetaminophen. However, 2 days later, she presented to the emergency department with severe pain over the allograft, oliguria, and increased JP drainage.
Initial laboratory studies performed in the emergency department showed:
SCr 3.5 mg/dL
Hemoglobin 9.1 g/dL
HCT 28%
Blood tacrolimus trough level 6 ng/mL (target trough level 10-12 ng/mL)
Urinalysis: 2+ blood, protein trace, 200 RBCs/HPF, 30 WBCs/HPF
JP drain fluid creatinine 50 mg/dL
Which one of the following is the MOST likely cause of AKI?

A. Acute antibody-mediated rejection

B. Urine leak

C. Obstructive uropathy due to a large lymphocele

D. Acute pyelonephritis

60. A 52-year-old female with a history of proteinuria and microscopic hematuria underwent a kidney biopsy that revealed moderate mesangial expansion and hypercellularity in 25 out of 25 glomeruli. Of the 25 glomeruli, one has fibrocellular crescent and five with endocapillary hypercellularity. Her kidney function has been stable with eGFR of 65 to 70 mL/min/1.73 m^2. Urinalysis reveals proteinuria of 200 mg/dL, 5 to 10 red blood cells per high powerfield, 0 to 3 white blood cells per high powerfield, and no casts. ANCA serology was negative.
Which one of the following is a CORRECT statement?

A. Patient has rapidly progressive glomerulonephritis (RPGN).

B. Patient likely has IgA nephropathy pending immunofluorescence confirmation.

C. Anti-glomerular basement membrane disease needs to be ruled out.

D. Patient likely has ANCA-associated GN.

61. A 57-year-old male with a history of chronic obstructive pulmonary disease, hypertension, type 2 diabetes mellitus, and chronic kidney disease stage G3b, presumably due to diabetic kidney disease, with relatively stable kidney function over the past 3 months asks about the appropriate timing of preparation for kidney replacement therapy (KRT) and referral for transplantation. Which ONE of the following may be used to determine the appropriate timing of preparation for KRT per KDIGO 2024?

A. eGFR below 15 mL/min/1.73 m^2

B. Volume overload requiring the use of loop diuretics

C. Serum albumin less than 3.5 g/dL

D. A 2-year kidney failure risk threshold of more than 40% using an externally validated risk equation

62. An 87-year-old nursing home resident with a history of hypertension and frequent falls is admitted to the hospital after being found down in the bathroom. Her medications include amlodipine and irbesartan.

Physical examination: older female, alert, pain score 3/10 over left knee

Vital signs: weight 62 kg, height body mass index 23 kg/m^2, BP 180/100 mm Hg, pulse 76 beats per minute, respiratory rate 16/min, temperature 37.2 °C

Neck: no lymphadenopathy, no bruits, no jugular vein distention

Oropharynx: within normal limits with moist oral mucosa

Lungs: clear to auscultation

Heart: 2/6 systolic nonradiating murmur over right upper sternal border

Abdomen: normal bowel sounds, soft, nondistended, nontender, no hepatosplenomegaly

Extremities: trace to 1+ bilateral ankle edema, full range of motion, mild-moderate pain of over left knee, no effusion
Deep tendon reflexes: symmetric, 2+ throughout
Neurologic examination: nonfocal
Which one of the following is the next BEST step?

A. Current high BP may reflect ongoing pain after fall. There is no need to intensify current antihypertensive regimen.
B. Add hydrochlorothiazide.
C. Add mineralocorticoid receptor antagonist (MRA).
D. Rule out pseudohypertension.

63. An 82-year-old female is brought to the clinic by her daughter for increasing memory loss. The patient lives by herself in an apartment. She has not seen any health care providers over the past 5 years and has no known medical history. She is not taking any medication. Review of systems is only notable for increasing forgetfulness that has been previously attributed to her age. She can still care for herself and shop for groceries down her street.
Physical examination: older lady, fragile but is alert and oriented to person, place, and situation, but not to date
Vital signs: weight 57 kg, body mass index 21 kg/m^2, BP 100/53 mm Hg, pulse 88 beats per minute, respiratory rate 19/min, temperature 36.8 °C
Oropharynx: within normal limits, moist mucosa
Lungs: clear to auscultation bilaterally
Heart: regular rate, normal S_1 and S_2; 1 to 2+ nonradiating systolic murmur over left sternal border
Abdomen: mildly distended, normal active bowel sounds, nontender to palpation; liver size 16 cm, no splenomegaly
Extremities: no edema
Deep tendon reflexes: symmetric, 2+ throughout, without delayed relaxation
Neurologic examination: nonfocal
Laboratory studies:

Hematology	Patient	Reference range
WBC count	5.2	4-10 × 10^3/mL
Hemoglobin	10.5	Female: 12-16 g/dL
Hematocrit	32.0	Female: 37%-48%; male: 45%-52%
Platelet count	169	150-350 × 10^3/mL
Mean corpuscular volume	101	80-100 fL
Metabolic profile		
Sodium	123	136-145 mmol/L
Potassium	3.2	3.5-5.0 mmol/L
Chloride	94	98-106 mmol/L
Total CO_2 (bicarbonate)	20	23-28 mmol/L
Anion gap	9	10-14 mmol/L
Blood urea nitrogen	6	8-20 mg/dL
Creatinine	0.6	0.7-1.3 mg/dL
Glucose (fasting)	98	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	2.9	3-4.5 mg/dL
Magnesium	1.6	1.5-2.4 mg/dL
Albumin	3.1	3.5-5.5 g/dL
Plasma osmolarity	262	275-295 mOsm/L
Lactate dehydrogenase	89	60-100 U/L
Liver function tests		

Hematology	Patient	Reference range
Total protein	5.8	6.0-7.8 g/dL
Albumin	3.4	3.5-5.5 g/dL
Alanine aminotransferase	34	0-35 U/L
Aspartate aminotransferase	69	0-35 U/L
Alkaline phosphatase	92	36-92 U/L
Total bilirubin	1.2	0.3-1.2 mg/dL
Direct bilirubin	0.3	0-0.3 mg/dL

Urinalysis		
Color	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.003	1.005-1.025
Glucose	0	≤130 mg/dL
Ketones	None	None
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Negative	Negative
Protein	Negative	≤150 mg/dL
Red blood cells (RBCs)	0-1	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	≤2-5 WBCs/HPF

Squamous epithelial cells	0	<15-20 squamous epithelial cells/HPF

Which one of the following is the MOST likely diagnosis?

A. Beer potomania

B. Primary adrenal insufficiency

C. Hypothyroidism

D. Syndrome of inappropriate relase of antidiuretic hormone

64. A 52-year-old male with antiphospholipase A2 receptor antibody–positive membranous nephropathy (MN), being treated with cyclophosphamide and glucocorticoid, presents for a routine follow-up. The patient endorses feeling well but notes recent marked increase in bilateral leg swelling. He denies any problem with urination. In addition to his immunosuppressive therapy, the patient also takes losartan 50 mg bid, bumetanide 2 mg daily, and atorvastatin 80 mg daily. His SCr and urine protein to creatinine ratio from his clinic visit 2 weeks prior was 1.2 mg/dL and 2.4 g/g, respectively.
Physical examination: well-appearing male, no acute distress
Vital signs: weight 109 kg, body mass index 37.7 kg/m^2, BP 138/70 mm Hg, pulse 77 beats per minute, respiratory rate 16/min, temperature 37.6 °C
Neck: flat neck vein, no lymphadenopathy
Oropharynx: moist oral mucosa
Lungs: clear to auscultation
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: normal bowel sounds, nondistended, nontender
Extremities: 3+ edema up to thighs bilaterally
Skin: warm, within normal limits
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	132	136-145 mmol/L
Potassium	4.7	3.5-5.0 mmol/L

Serum chemistry	Patient	Reference range
Chloride	105	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Anion gap	6	10-14 mmol/L
Blood urea nitrogen	43	8-20 mg/dL
Creatinine	2.9	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	45	mL/min/1.73 m^2
Glucose (fasting)	98	70-100 mg/dL
Liver function tests		
Total protein	5.4	6.0-7.8 g/dL
Albumin	1.5	3.5-5.5 g/dL
Urinalysis		
Color	Dark yellow to brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.017	1.005-1.025
Glucose	Trace	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL

Serum chemistry	Patient	Reference range
Blood	Positive	Negative
Protein	>600	≤150 mg/dL
Red blood cells (RBCs)	20-30	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	None	None

Urine protein to creatinine ratio 8.1 g/g
What is the next BEST step?

A. Increase bumetanide to 2 mg bid.

B. Hold losartan.

C. Increase bumetanide to 2 mg bid and hold losartan.

D. Obtain renal vein Doppler.

65. Oxalate nephropathy can occur after chronic or excessive ingestion of all of the following EXCEPT:

A. Aristolochic acid

B. Starfruit

C. Rhubarb

D. Cranberry concentrate tablets

66. A 54-year-old female with type 2 diabetes mellitus for over 10 years complicated by chronic kidney disease stage G3bA3 and proliferative diabetic retinopathy, heart failure with preserved ejection fraction gout, and HTN presents to clinic for routine follow-up. The patient endorses following a healthy and active lifestyle over the past 3 months.
Medications: atorvastatin, metformin, empagliflozin, losartan, eplerenone

Vital signs: BP 127/76 mm Hg, pulse 78 beats per minute
Physical examination: heart, lungs, abdomen are within normal limits. There is trace pedal edema bilateral lower extremities. Neurologic examination is nonfocal.
Laboratory studies reveal eGFR 38 mL/min/1.73 m^2, hemoglobin A1C (HbA1C) 7.8%, urinalysis is bland without cells or casts. Urine albumin to creatinine ratio is 3.5 g/g.
Which ONE of the following agents may be added for better glycemic control while providing renoprotection and cardiovascular benefits?

A. α-Glucosidase inhibitors (eg, acarbose, miglitol, voglibose)
B. Long-acting glucagon-like peptide 1 receptor agonist (GLP-1 RA) (eg, liraglutide, semaglutide, dulaglutide)
C. Dipeptidyl peptidase 4 inhibitor (DPP-4i) (eg, saxagliptin, alogliptin)
D. Thiazolidinedione

67. A 54-year-old male with a history of end stage kidney disease from Mesoamerican nephropathy, requiring peritoneal dialysis support, presents with acute onset of left shoulder pain. He denies any associated fevers, chills, nausea, vomiting, or diaphoresis. Physical examination is negative for any chest wall tenderness. Both shoulders have normal range of motion without any focal tenderness or joint effusion. Heart and lungs are within normal limits. Extremities have no edema.
Electrocardiogram and troponin are both negative.
Radiograph of the left shoulder is unremarkable.
Chest radiograph is within normal limits.
Which one of the following is the next BEST step?

A. Perform cardiac catheterization.
B. Rule pulmonary embolism.
C. Obtain a chest radiograph.
D. Infuse full exchange volume, then drain dialysate with the patient in knee-chest position.

68. A 61-year-old male truck driver is referred to your hypertension clinic for persistent HTN despite being on multiple medications. His medical history is also notable for hyperlipidemia.
Medications: amlodipine 10 mg qd, chlorthalidone 25 mg qd, benazepril 40 mg qd, carvedilol 25 mg bid, atorvastatin 80 mg qhs
Vital signs: BP 192/105 mm Hg, pulse 89 beats per minute. The patient appears euvolemic. Physical examination is unremarkable. Extremities are without edema.
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	142	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	106	98-106 mmol/L
Total CO_2 (bicarbonate)	24	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	17	8-20 mg/dL
Creatinine	1.24	0.7-1.3 mg/dL
Glucose (fasting)	105	70-100 mg/dL
Calcium	9.6	9-10.5 mg/dL
Phosphorus	4.2	3-4.5 mg/dL
Magnesium	2.2	1.5-2.4 mg/dL

Assuming the patient's high BP has been confirmed at multiple clinic visits, which one of the following is the next BEST step?

A. Obtain an Electrocardiogram.

B. Check pill count.

C. Add spironolactone.

D. Switch amlodipine to nifedipine.

69. A 52-year-old male who is morbidly obese presents with a history of fatigue and total body pain. He has been trying to lose weight and has adopted a healthy lifestyle with daily moderate exercise. His medications include orlistat, vitamin C, and sodium glucose cotransporter 2 inhibitor (SGLT2i). His routine laboratory studies are notable for mild acute kidney injury, with serum creatinine increased to 1.6 mg/dL from 0.9 mg/dL 4 weeks ago.
His urine studies are as follows:

	Patient	Normal range
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	6.0	4.5-8.0
Specific gravity	1.021	1.005-1.025
Glucose	Trace	Negative
Ketones	Positive	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Negative	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	0-1	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-1	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF

	Patient	Normal range
Casts	None	None

Urine protein to creatinine ratio 5.5 g/g
Urine albumin to creatinine ratio 0.25 g/g
Which one of the following is the MOST likely diagnosis?

A. Orlistat-induced calcium oxalate stone formation

B. Vitamin C–associated calcium oxalate stone formation

C. SGLT2i-induced acute tubular injury

D. Paraproteinemia such as multiple myeloma

70. A 76-year-old female with a history of osteoarthritis of bilateral knees is referred for increasing fatigue and acute kidney failure. Her only medication is acetaminophen as needed for knee pain. Laboratory studies:

Hematology	Patient	Reference range
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	10.1	Female: 12-16 g/dL
Hematocrit	30.5	Female: 37%-48%
Platelet count	217	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Serum chemistry		
Sodium	140	136-145 mmol/L
Potassium	5.6	3.5-5.0 mmol/L
Chloride	108	98-106 mmol/L
Total CO_2 (bicarbonate)	20	23-28 mmol/L
Anion gap	12	10-14 mmol/L

Hematology	Patient	Reference range
Blood urea nitrogen	135	8-20 mg/dL
Creatinine	8.8 (1.2, 6 mo prior)	0.7-1.3 mg/dL
Glucose (fasting)	98	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	9.9	3-4.5 mg/dL
Albumin	3.0	3.5-5.5 g/dL
Urinalysis		
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.022	1.005-1.025
Glucose	Trace	Negative
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Positive	Negative
Protein	100 mg/dL	Negative
Red blood cells (RBCs)	0-3	≤2 RBCs/High power field (HPF)
White blood cells	0-3	≤2-5 WBCs/HPF

Hematology	Patient	Reference range
(WBCs)		
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	0-5 granular casts	None

24-hour urine creatinine 1,200 mg, protein 8.7 g, albumin 0.72 g
Serum λ chain 7,657 mg/dL, κ/λ ratio less than 0.001
Which one of the following is the MOST likely cause of kidney injury?

A. Light chain cast nephropathy

B. Light chain deposition disease

C. AL amyloidosis

D. Acute tubular injury

71. A 54-year-old female with a history of autoimmune hepatitis presents with rapidly increasing abdominal girth and marked bilateral lower extremity swelling over the past month. Medical history is otherwise negative. She has not been taking any medication. Review of systems is notable for reduced appetite and yellowing of skin.
Physical examination
Vital signs: weight 75 kg, BP 99/52 mm Hg, pulse 98 beats per minute, respiratory rate 20/min, temperature 36.6 °C
General: thin woman, chronically ill appearing in no acute distress, alert and oriented to date, person, place, and situation
Head and neck: notable for icteric sclera
Oropharynx: within normal limits with moist oral mucosa
Lungs: clear to auscultation
Heart: regular rate, normal S_1 and S_2, no murmurs, gallops, or rubs
Abdomen: markedly distended and tense but nontender to palpation. Bowel sounds are normal. Liver size is 14 cm. Splenomegaly is noted.

Extremities: 2+ edema up to thighs bilaterally
Skin: marked jaundice.
Deep tendon reflexes: symmetric, 2+ throughout, without delayed relaxation
Laboratory studies:

Metabolic profile on admission	Patient	Reference range
Sodium	125	136-145 mmol/L
Potassium	4.7	3.5-5.0 mmol/L
Chloride	101	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	6	10-14 mmol/L
Blood urea nitrogen	22	8-20 mg/dL
Creatinine	1.5	0.7-1.3 mg/dL
Glucose (fasting)	71	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	2.9	3-4.5 mg/dL
Magnesium	1.8	1.5-2.4 mg/dL
Plasma osmolarity	280	275-295 mOsm/L
Lactate dehydrogenase	56	60-100 U/L

Upon admission, the patient receives intravenous bumetanide, uptitrated to 4 mg 6 times daily along with spironolactone 100 mg bid and 25 g of 25% albumin tid, but her urine output remains below 400 mL/d. A diagnostic paracentesis performed on admission shows no evidence of malignancy or peritonitis. Over the next 3 days, her creatinine continues to increase, with the most recent value being 3.2 mg/dL. Her serum sodium remains in the low 120s. The patient appears more fatigued since admission.

Her oxygen saturation has been noted to decrease to the low 90% despite having a higher respiratory rate over the last 2 days. What is the next BEST step?

A. Perform a large-volume paracentesis.

B. Increase 25% albumin infusion to 25 g qid.

C. Infuse 200 mL of 3% saline solution.

D. Provide terlipressin.

72. A 51-year-old male science teacher is referred to your HTN clinic for persistent HTN despite being on multiple medications. He has no other medical history.
Medications: nifedipine 60 mg qd, benazepril 40 mg qd, isosorbide mononitrate 60 mg qd, hydralazine 50 mg tid
Vital signs: BP 162/95 mm Hg, pulse 94 beats per minute. Physical examination is unremarkable. Extremities with trace to 1+ edema above ankles bilaterally.
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	142	136-145 mmol/L
Potassium	4.6	3.5-5.0 mmol/L
Chloride	105	98-106 mmol/L
Total CO_2 (bicarbonate)	24	23-28 mmol/L
Anion gap	13	10-14 mmol/L
Blood urea nitrogen	12	8-20 mg/dL
Creatinine	1.10	0.7-1.3 mg/dL
Glucose (fasting)	100	70-100 mg/dL
Calcium	9.8	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL

Serum chemistry	Patient	Normal range
Magnesium	2.1	1.5-2.4 mg/dL

Which one of the following BEST characterizes this patient's hypertension (HTN)?

A. Drug-resistant HTN

B. Refractory HTN

C. Apparent resistant HTN

D. Pseudoresistant HTN

73. A 62-year-old female with a history of depression, type 2 diabetes mellitus, and hypertension is brought to the emergency department by her son for failure to thrive. Review of systems is notable for reduced appetite and slow mentation.
Medications: chlorthalidone 12.5 mg daily (added 3 weeks ago due to poorly controlled blood pressure and mild hyperkalemia), losartan 50 mg bid, metformin 500 mg bid, quetiapine 100 mg daily (started 6 months ago), one tablet of multivitamin daily
Physical examination: older than stated age woman who appears chronically ill
Vital signs: weight 61 kg, BP 148/82 mm Hg, pulse 82 beats per minute, respiratory rate 16/min, temperature 37.2 °C
Head and neck: within normal limits; moist oral mucosa
Heart, lungs, abdomen: within normal limits
Extremities: no edema
Neurologic: slow mentation, otherwise nonfocal. Deep tendon reflexes are 1 to 2+ throughout, symmetric. No delayed relaxation.
Urine output over the first 24 hours of admission is 800 mL.
Laboratory studies:

Metabolic profile on admission	Patient	Reference range
Sodium	117 (135, 1 mo ago)	136-145 mmol/L
Potassium	3.7	3.5-5.0 mmol/L

Metabolic profile on admission	Patient	Reference range
Chloride	87	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	5	8-20 mg/dL
Creatinine	1.1	0.7-1.3 mg/dL
Glucose (fasting)	157	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	4.2	3-4.5 mg/dL
Magnesium	1.7	1.5-2.4 mg/dL
Plasma osmolarity	252	275-295 mOsm/L
Lactate dehydrogenase	43	60-100 U/L

Urine studies: osmolality 395 mOsm/kg, sodium less than 10 mmol/L, potassium 19 mmol/L

Which one of the following is the next BEST step?

A. Discontinue metformin.

B. Discontinue chlorthalidone.

C. Discontinue quetiapine.

D. Fluid restriction.

74. Which one of the following statements is CORRECT?

A. Cyclosporine is more diabetogenic than tacrolimus.

B. Belatacept is more diabetogenic than tacrolimus.

C. Mammalian target or rapamycin (mTOR) inhibitors are nondiabetogenic.

D. Unlike the calcineurin inhibitors, belatacept is nonnephrotoxic.

75. A 47-year-old female with a history of type 2 diabetes mellitus, chronic kidney disease stage 3bA3, and heart failure with preserved ejection fraction is planned for an elective laparoscopic cholecystectomy in 1 week.
Medications: atorvastatin, icosapent ethyl, metformin, canagliflozin, irbesartan, furosemide
Which one of the following statements is CORRECT regarding the use of an sodium glucose cotransporter 2 inhibitor (SGLT2i)?
    A. Discontinue SGLT2i when eGFR falls below 20 mL/min/1.73 m^2 even if the patient has been safely tolerating the medication.
    B. It is reasonable to hold SGLT2i during prolonged fasting, surgery, or critical medical illness due to concerns for increased risk for euglycemic DKA.
    C. The use of SGLT2i is contraindicated in individuals with HF requiring chronic loop diuretic use.
    D. Once initiated, it is reasonable to continue SGLT2i even when KRT is initiated.
76. A 67-year-old female from Southeast Asia is brought to the emergency department by her daughter for a fall and fractured right forearm. Her daughter reports that she is a vegan but generally eats well. Review of systems is notable for cold intolerance over the years that has been attributed to the colder weather in North America. She is currently on no medication. Her past medical/surgical history is notable for a complicated pregnancy years ago due to placenta abruptio.
Physical examination: well appearing and pleasant
Vital signs: weight 51 kg, BP 108/62 mm Hg, pulse 60 beats per minute, respiratory rate 16/min, temperature 35.6 °C
Head and neck are within normal limits.
Oropharynx has moist oral mucosa.
Heart, lungs, and abdomen are within normal limits.
Extremities have no edema.
Neurologic examination is notable for slow mentation, otherwise nonfocal. Deep tendon reflexes are symmetric and 1+ throughout

with delayed relaxation.
Laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	122	136-145 mmol/L
Potassium	3.7	3.5-5.0 mmol/L
Chloride	88	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	11	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	107	70-100 mg/dL
Calcium	9.0	9-10.5 mg/dL
Phosphorus	3.9	3-4.5 mg/dL
Magnesium	1.8	1.5-2.4 mg/dL
Plasma osmolarity	262	275-295 mOsm/L
Lactate dehydrogenase	76	60-100 U/L

Morning cortisol 5 (normal 5-25 µg/dL)
Thyroid-stimulating hormone 2.4 mIU/L (normal 0.4-4.0)
Urine studies: osmolality 395 mOsm/kg, sodium 31 mmol/L, potassium 21 mmol/L
What is the next BEST diagnostic test?

A. Free T4 (thyroxine) level

B. Adrenocorticotropin hormone level

C. Plasma aldosterone levels

D. Copeptin level

77. A 58-year-old Asian female with a history of unilateral renal agenesis is referred to your clinic for persistent hypertension despite being on multiple medications. She has no other medical history. Your office has confirmed her persistently elevated BP, medication adherence, and healthy lifestyle modification. The patient is adamant about not taking more than three medications at this time. She reports intolerance to nifedipine previously.
Medications: amlodipine 10 mg qd, losartan 50 mg bid, hydrochlorothiazide 25 mg qd
Vital signs: weight 65 kg, average continuous ambulatory blood pressure 137/85 mm Hg, pulse 67 beats per minute. Physical examination is unremarkable. Extremities have trace ankle edema bilaterally.
Laboratory studies:

Serum chemistry	**Patient**	**Normal range**
Sodium	138	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	102	98-106 mmol/L
Total CO_2 (bicarbonate)	23	23-28 mmol/L
Anion gap	13	10-14 mmol/L
Blood urea nitrogen	9	8-20 mg/dL
Creatinine	0.9	0.7-1.3 mg/dL
Glucose (fasting)	97	70-100 mg/dL
Calcium	9.4	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL
24-h urine		

Serum chemistry	Patient	Normal range
Creatinine	1,350	Women: 15-20 mg/kg/24 h
Volume	978	Variable
Sodium	90	mmol (variable)

Which one of the following is the next BEST step?

A. Change hydrochlorothiazide to chlorthalidone or indapamide.

B. Change losartan to an angiotensin converting enzyme inhibitor (ACEi) such as benazepril.

C. Change amlodipine to nifedipine.

D. Emphasize adherence to dietary sodium restriction.

78. Which one of the following statement(s) is/are TRUE regarding amyloidosis and fibrillary glomerular disorders?

A. AA amyloid is the most common secondary form of amyloid, associated with chronic infections (tuberculosis being one of the most common causes outside North America), as well as chronic inflammatory diseases (familial Mediterranean fever, rheumatoid arthritis).

B. LECT2 amyloid is almost as frequent as AA amyloid, particularly in patients of Hispanic or Middle Eastern ethnicity.

C. Fibrillary glomerulonephropathy (GN) is a very rare proliferative form of GN associated with the presence of the protein DnaJ heat shock protein family member B9 (DNAJB9). Fibrillary GN is not associated with monoclonal gammopathy and is thought to be a distinct unrelated condition from immunotactoid GN.

D. All the above are correct.

79. A 47-year-old female with a history of autosomal recessive Alport syndrome and hypertension presents with proteinuria, microscopic hematuria, and eGFR of 42 mL/min/1.73 m^2. Physical examination is unremarkable.
A kidney biopsy is performed. Light microscopy showed focal and segmental glomerulosclerosis (FSGS) pattern of injury with

moderate interstitial fibrosis and tubular atrophy. Electron microscopy revealed glomerular basement membrane with irregular thinning and thickening, layered or lamellated "basket-weave" appearance in thickened areas. There are no electron dense deposits.

Which one of the following is a CORRECT statement?

A. Primary or familial FSGS can be ruled out when FSGS is seen in the kidney biopsy of patients with Alport syndrome.
B. When Alport syndrome is complicated by FSGS, rapid kidney function decline can be slowed down with glucocorticoid (GC) therapy.
C. Alport syndrome may be complicated by the FSGS pattern of injury.
D. Alport syndrome complicated by FSGS is only seen with mutations involving the α5 chain of type 4 collagen.

80. A 62-year-old male with a history of chronic kidney disease stage G3aA3 presumably due to prior chronic use of NSAIDs presents to your hypertension clinic for routine care. His systolic blood pressure has been ranging from 130 to 140 mm Hg and diastolic blood pressure from 80 to 85 mm Hg over the last three clinic visits. The patient endorses following a healthy and active lifestyle over the past 4 months.

Assuming the same blood pressure readings in out-of-office, what is the BEST management strategy?

A. No treatment is needed. The patient is at BP goal.
B. Start an angiotensin receptor antagonist.
C. Continue with healthy lifestyle modification and return in 3 months.
D. Start a β-blocker.

81. KDIGO suggests using an externally validated risk equation (eg, online calculators from Kidneyfailurerisk.com, http://ckdpcrisk.org/lowgfrevents/) to assess future risks for kidney failure and cardiovascular complications and mortality, and

management planning in patients with chronic kidney disease stages G3 to G5.

Which ONE of the following are basic predictors that are consistently used in well-validated risk-predicting equations?

A. Age, gender, current eGFR, and urine albumin to creatinine ratio

B. Age, gender, current SCr and cystatin values, and urine protein to creatinine ratio (uPCR)

C. Age, gender, current eGFR, and uPCR

D. Age, gender, current eGFR, and low-density lipid cholesterol

82. A 27-year-old female with end stage kidney disease who has been on peritoneal dialysis (PD) for 2 years presents with pregnancy at 4-week gestational age.

Which one of the following is the BEST advice for this patient receiving PD?

A. Switch peritoneal dialysis (PD) to hemodialysis (HD).

B. Start low-dose aspirin daily.

C. The well-established recommended dose of total small solute clearance should be K_t/V_{urea} 1.7/wk or higher.

D. Advise patient to remain on PD because birth weight tends to be greater with PD than with HD.

83. Which one of the following statements regarding pain medications is CORRECT?

A. Morphine and its active metabolite can accumulate in patients with chronic kidney disease (CKD). However, with close clinical monitoring, morphine can be safely used in patients with CKD.

B. Both gabapentin and pregabalin are metabolized by the liver and do not need dose adjustment in patients with CKD.

C. Tramadol is hepatically metabolized, and its use is safe in patients with CKD.

D. Fentanyl is rapidly metabolized in the liver. There does not appear to be any clinically significant accumulation of fentanyl

in patients with advanced CKD.

84. Which one of the following statements regarding post-transplantation lymphoproliferative disorder (PTLD) is CORRECT?
    A. Prior history of PTLD is a contraindication to reallograft transplant.
    B. First-line therapy for Epstein-Barr virus (EBV)-positive PTLD should be immunosuppression reduction and initiation of acyclovir or ganciclovir.
    C. Chemotherapy is currently considered standard therapy for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone.
    D. EBV donor-recipient mismatch is the most well-established risk factor.
85. Which one of the following is CORRECT regarding cytomegalovirus (CMV) infection in the post-transplantation period?
    A. Primary CMV infection is usually more severe than reactivated infection or superinfection.
    B. Undetectable serum CMV DNA by quantitative nucleic acid testing (QNAT) rule out invasive CMV disease (such as gastritis or colitis).
    C. CMV prophylaxis is not required in CMV-seropositive recipient, regardless of donor CMV serostatus (ie, whether donor CMV IgG is negative or positive).
    D. Asymptomatic CMV DNAemia does not require treatment, regardless of CMV DNA titer.
86. A 45-year-old female with a history of obesity and HTN comes to you for advice on healthy lifestyle modification.
    Which one of the following statements is CORRECT?
    A. Losing 10 kg body may reduce her systolic blood pressure by 10 mm Hg.
    B. Moderate exercise (eg, 30-minute brisk walk daily, most days of week, or 150-min/wk) reduces the risk of cardiovascular

events, but not blood pressure (BP).

C. Adopt Dietary Approaches to Stop Hypertension (DASH)-like eating plan may increase the risk of dementia.

D. Dietary sodium restriction less than 2 g/d is the most effective strategy in reducing BP.

87. Which of the following is the CORRECT antidote to the drugs listed?

A. Andexanet: rivaroxaban

B. Phytonadione: heparin

C. Protamine: warfarin

D. Andexanet: dabigatran

E. Idarucizumab: apixaban

88. A 45-year-old male with no past medical history presents with generalized weakness and reduced urine output over 1 week. The patient denies taking any medication or recreational drug. His serum creatinine 2 months prior was 1.2 mg/dL and calcium was 10.2 mg/dL. Physical examination is unremarkable.
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	6.7	4-10 × 10^3/mL
Hemoglobin	13.5	Male: 14-17 g/dL
Hematocrit	41.0	Male: 45%-52%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Reticulocyte count	0.7	0.5%-1.5% of erythrocytes
Haptoglobin	215	50-220 mg/dL
Serum chemistry		
Sodium	132	136-145 mmol/L

Hematology	Patient	Reference range
Potassium	6.2	3.5-5.0 mmol/L
Chloride	96	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	18	10-14 mmol/L
Blood urea nitrogen	178	8-20 mg/dL
Creatinine	15.7	0.7-1.3 mg/dL
Glucose (fasting)	78	70-100 mg/dL
Calcium	5.6	9-10.5 mg/dL
Phosphorus	11.4	3-4.5 mg/dL
Magnesium	2.3	1.5-2.4 mg/dL
Urinalysis		
Color	Dark brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.011	1.005-1.025
Glucose	Trace	≤130 mg/dL
Ketones	Positive	None
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Positive	Negative
Urobilirubin	2	0.5-1.0 mg/dL

Hematology	Patient	Reference range
Blood	Large	Negative
Protein	200	≤150 mg/dL
Red blood cells (RBCs)	0-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	2-5	<15-20 squamous epithelial cells/HPF
Casts	None	None

Kidney ultrasound with normal-appearing kidneys without hydronephrosis, stone, mass, or cyst

What is the MOST likely cause for this patient's hypocalcemia?

A. Secondary hyperparathyroidism (hPTH)

B. Nephrogenic diabetes insipidus

C. Deposition in injured soft tissue

D. Loss-of-function mutation involving fibroblast growth factor 23 (FGF-23)

89. A 61-year-old female with ESKD due to IgA nephropathy received a deceased donor kidney transplant 4 months ago. She presents to clinic for a routine follow-up visit. The patient reports feeling well and has no complaints. Her current medications include tacrolimus 2 mg bid, mycophenolate mofetil 500 mg bid (dose reduced from 1,000 mg bid 4 weeks ago due to BK polyomavirus DNAemia), prednisone 5 mg daily, diltiazem extended-release (XR) 180 mg daily, valganciclovir 900 mg daily, trimethoprim-sulfamethoxazole single strength daily, and pantoprazole 40 mg daily. On physical examination, her vital signs are within normal range and at her baseline. She has trace peripheral edema bilaterally. The rest of her physical examination is unremarkable. The allograft is palpable in the right lower quadrant. There is no tenderness over the allograft.

Laboratory studies:

Serum chemistry	Patient	Reference range
Creatinine	0.9 (baseline 0.9-1.1 mg/dL)	0.7-1.3 mg/dL
Calcium	9.8	8.6-10.4 mg/dL
Phosphorus	2.0	2.3-3.4 mg/dL
Magnesium	1.1	1.4-1.9 mg/dL

Liver function test and complete blood count are within normal range.
Plasma CMV DNA less than 35 copies/mL (reference range: not detected)
Plasma BKPyV DNA 10,200 copies/mL (1,500 copies 4 weeks ago; reference range: not detected)
Urinalysis: negative for protein, trace blood, 10 RBCs/HPF, 2 WBCs/HPF
Which one of the following is the BEST management strategy?

A. Further immunosuppression reduction (such as holding mycophenolate mofetil with or without simultaneous lowering of tacrolimus target goal level)
B. Further immunosuppression reduction and start fluoroquinolone
C. Mycophenolate mofetil to sirolimus (or everolimus) switch
D. Intravenous immunoglobulin (IVIG)

90. A 58-year-old female with known white coat hypertension (WCH) with office blood pressure (BP) ranging from 150-160/90-100 mm Hg and home BP ranging from 120-130/70-80 mm Hg on no antihypertensive agents presents to you for your expert opinion regarding her BP management. She has done her best with maintaining a healthy lifestyle over the past 3 months.
Which one of the following is the BEST advice for her?

A. Assure her that she only has WCH, which is benign.
B. Obtain an electrocardiogram or two-dimensional echocardiogram.

C. Start an angiotensin receptor blocker (ARB).

D. Encourage dietary sodium restriction to below 100 mmol/d (2.3 g).

91. You are consulted by the medicine team for a case of rapidly over correction of hyponatremia. The patient is a 57-year-old female weighing 60 kg with newly diagnosed panhypopituitarism when she presented to the hospital with fatigue. Her baseline serum sodium was 122 mmol/L. Despite free water restriction, her serum sodium did not correct. The day prior to consulting you, the patient was started on intravenous levothyroxine and hydrocortisone by the endocrinology service. Within 24 hours, a repeat serum sodium increased to 127, then 130, then 134 mmol/L. Her 24-hour fluid intake was documented as 1.2 L. No urine output was recorded.
What is the MOST likely reason for this overly rapid correction of hyponatremia?

A. Undocumented infusion of 3% saline by primary care provider

B. She has chronic polydipsia and polyuria and did not report all her fluid intake to the nursing staff.

C. She developed aquaresis overnight.

D. Lab error: repeat chemistry

92. A 54-year-old female with a history of hypertension presents for a routine clinic follow-up. She only complains of bilateral ankle swelling.
Medications include amlodipine 10 mg daily and chlorthalidone 12.5 mg daily.
Physical examination: well-appearing female in no acute distress
Vital signs: weight 60 kg, BP 142/85 mm Hg, pulse 85 beats per minute, respiratory rate 20/min, temperature 37.2 °C
Head and neck: within normal limits; dry oral mucosa
Lungs: clear to auscultation
Heart: normal S_1 and S_2, no murmurs, gallops, or rubs
Abdomen: normal active bowel sounds, soft, nondistended, nontender

Extremities: 1+ bilateral ankle edema

Metabolic profile	Patient	Reference range
Sodium	135	136-145 mmol/L
Potassium	3.4	3.5-5.0 mmol/L
Chloride	99	98-106 mmol/L
Total CO_2	24	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	11	8-20 mg/dL
Creatinine	1.1	0.7-1.3 mg/dL
Glucose (fasting)	87	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL
Albumin	4.2	3.5-5.5 g/dL

Urinalysis is bland without protein or blood.
Which one of the following is the next BEST step to improve the edema while minimizing polypharmacy?

A. Increase chlorthalidone to 25 mg daily.

B. Switch amlodipine to nifedipine.

C. Add a β-blocker.

D. Switch chlorthalidone to an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

93. A 27-year-old female chemistry graduate student with no past medical history presents with acute onset of periorbital edema 2 weeks prior that has since progressed to anasarca. The patient

has not been taking any medications. Family history and social history are noncontributory.
Physical examination: well-appearing female
Vital signs: weight 79 kg, height 1.70 m, BP 102/64 mm Hg, pulse 78 beats per minute, respiratory rate 16/min, temperature 37.5 °C
Neck: flat neck vein, no lymphadenopathy
Oropharynx: moist oral mucosa
Lungs: clear to auscultation
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: normal bowel sounds, nondistended, nontender, +1 edema
Extremities: 3+ edema up to thighs bilaterally
Skin: warm, no rash
Laboratory studies reveal serum creatinine 2.1 mg/dL (baseline from 2 months prior was 0.8 mg/dL), albumin 2.5 mg/dL, and total cholesterol 289 mg/dL. urine protein to creainine ratio is 7 g/g. Urinalysis is notable for specific gravity 1.022, 5 to 10 hyaline casts and 2 to 5 RBCs/HPF. Hemoglobin is 16.7 g/dL.
Kidney ultrasound: left kidney 13.5 cm, right kidney 12.5 cm, normal corticomedullary differentiation, no hydronephrosis, cysts, or stones
Preliminary kidney biopsy read suggests minimal change disease (MCD).
Which one of the following is the MOST effective agent to improve the patient's AKI?

A. Loop diuretic

B. Intravenous fluid

C. 25% albumin infusion

D. Angiotensin receptor blocker

94. A 55-year-old male with end stage kidney disease from chronic interstitial nephritis, hemodialysis dependent, hypertension, hyperlipidemia, HF with ejection fraction of 25% to 30% due to ischemic heart disease, and granulomatous disease–associated hypercalcemia who presents frequently to the dialysis unit with

hyperkalemia and volume overload due to dietary nonadherence. Review of systems is notable for a history of constipation.

Which one of the following is the BEST preventive agent against hyperkalemia to use in this patient?

A. Sodium polystyrene sulfonate (SPS)—cation exchange resin (Kayexalate)

B. Patiromer (Veltassa)—synthetic polymer with Ca^{2+} as exchange counterion

C. Sodium zirconium cyclosilicate (Lokelma-Na^{+}-K^{+} cation exchanger)

D. Use of laxative such as PEG-3350 (MiraLax)

95. A 35-year-old female with type 1 diabetes mellitus was admitted for a fungating mass affecting the clivus and cervical vertebrae, presumed to be invasive mucormycosis. On hospital day 1, the patient was initiated on liposomal amphotericin (10 mg/kg) with normal saline support. On day 4, sulfamethoxazole/trimethoprim and ampicillin/sulbactam were added for methicillin-sensitive *Staphylococcus aureus* and *Prevotella buccae* cultured from the fungating mass. On day 10, the patient was noted to have an elevated creatinine, which increased from 0.5 to 1.46 mg/dL concurrently with a progressive rise in serum phosphorus up to 10.7 mg/dL. Other notable electrolyte disturbances include hypokalemia (3.1 mmol/L) and hypomagnesemia (1.2-1.3 mg/dL). Uric acid level was 2.3 mg/dL.

Urinalysis is bland without proteinuria, blood, glucose, or cells.

What is the BEST management strategy for progressive hyperphosphatemia?

A. Start phosphate binder.

B. Discontinue sulfamethoxazole/trimethoprim.

C. Discontinue ampicillin/sulbactam.

D. Call the lab and ask for possible technical error.

96. HLA allosensitization can occur through all of the following EXCEPT:

A. Blood transfusion and prior organ transplantation

B. Pregnancy

C. Following infection or following surgical procedures

D. All of the above

97. A 45-year-old male with a history of depression is brought to the clinic by his family for an acute anxiety attack. He has not been taking any new medication or recreational drug.
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	7.7	4-10 × 10^3/mL
Hemoglobin	13.8	Male: 14-17 g/dL
Hematocrit	41.5	Male: 45%-52%
Platelet count	217	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Reticulocyte count	0.7	0.5%-1.5% of erythrocytes
Haptoglobin	215	50-220 mg/dL
Serum chemistry		
Sodium	142	136-145 mmol/L
Potassium	3.7	3.5-5.0 mmol/L
Chloride	111	98-106 mmol/L
Total CO_2 (bicarbonate)	19	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	8	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL

Hematology	Patient	Reference range
Glucose (fasting)	78	70-100 mg/dL
Calcium	9.7	9-10.5 mg/dL
Phosphorus	1.9	3-4.5 mg/dL
Magnesium	1.8	1.5-2.4 mg/dL

Venous blood gas: pH 7.5, pCO_2 25 mm Hg

What is the next BEST step in managing this patient's hypophosphatemia?

A. Start calcitriol.

B. Start anxiolytic.

C. Infuse 30 mmol potassium phosphate.

D. Obtain fibroblast growth factor 23 level.

98. A 55-year-old female with a history chronic kidney disease (CKD) stage G4A2 due to chronic interstitial nephritis presumed to be due to the chronic use of NSAIDs and hypertension (HTN). She complains of polypharmacy prescribed for her multiple complications associated with CKD. Despite living a healthy and active lifestyle and maintaining adherence to all prescribed medications, her systolic blood pressure remains in the range of 130 to 140 mm Hg. Physical examination is within acceptable limits. Lower extremities are without edema.

Her current medications include irbesartan, chlorthalidone, amlodipine, spironolactone, omeprazole, atorvastatin, sevelamer carbonate, cholecalciferol, and erythropoiesis-stimulating agent (ESA).

Which one(s) of the following statements is/are CORRECT regarding HTN in patients with CKD?

A. The combined use of an angiotensin receptor blocker (ARB) and mineralocorticoid receptor anta gonist (MRA) is contraindicated in patients with CKD and HTN.

B. Thiazide diuretics such as chlorthalidone are ineffective in patients with CKD stage 4 and should be discontinued once patients reach stage 4 CKD.

C. In patients who are nondiabetic who have HTN, CKD, and severe albuminuria (ie, G1-G4, A3), the use of an angiotensin converting enzyme inhibitor or ARB is *recommended*.

D. All the above are correct.

99. Which one of the following is CORRECT regarding focal segmental glomerulosclerosis (FSGS) recurrence after transplantation?

A. FSGS associated with APOL1 high-risk variants has a high risk of recurrence after transplantation.

B. Collapsing FSGS variant has the highest risk of recurrence after transplantation.

C. Familial FSGS has a high risk of recurrence after transplantation.

D. High level of proteinuria is a risk factor for FSGS recurrence.

00. A 67-year-old male with a history of coronary artery disease, hypertension, and anuric ESKD requiring HD support every Monday, Wednesday, and Friday presents on Tuesday for a scheduled bilateral lower extremity angiogram for a history of worsening claudication.

Physical examination: well-appearing male, no acute distress

Vital signs: weight 109 kg, height 1.70 m, body mass index 37.7 kg/m^2, BP 138/70 mm Hg, pulse 77 beats per minute, respiratory rate 16/min, temperature 37.6 °C

Neck: no jugular venous distention or lymphadenopathy

Oropharynx: moist oral mucosa

Lungs: clear to auscultation

Heart: normal S_1, S_2, $+S_3$

Abdomen: normal bowel sounds, nondistended, nontender

Extremities: no pedal edema

Skin: warm, within normal limits

Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	132	136-145 mmol/L
Potassium	4.7	3.5-5.0 mmol/L
Chloride	105	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Anion gap	6	10-14 mmol/L
Blood urea nitrogen	43	8-20 mg/dL
Creatinine	4.9	0.7-1.3 mg/dL
Glucose (fasting)	98	70-100 mg/dL

Which one of the following is the BEST strategy to manage this patient's hemodialysis (HD) treatment?

A. Perform HD immediately after contrast study.

B. Perform HD immediately after contrast study in addition to patient's routine HD session on Wednesday.

C. Wait until Wednesday to perform patient's HD per routine.

D. Perform continuous kidney replacement therapy immediately after contrast study for 24 hours.

01. A 68-year-old female with chronic kidney disease stage G4A3 due to immune complex–mediated membranoproliferative glomerulonephritis (MPGN) complicated by secondary hyperparathyroidism and anemia presents for routine follow-up. She denies having any problem with her energy level or daily activities, dyspnea on exertion, short of breath, or chest pain. Laboratory studies:

Hematology	Patient	Reference range
White blood cell count	4	4-10 × 10^3/mL
Hemoglobin	9.5	Female: 12-16 g/dL

Hematology	Patient	Reference range
Hematocrit	28.8	Female: 37%-48%
Platelet count	249	150-350 × 10^3/mL
Mean corpuscular volume	80	80-100 fL
Reticulocyte count	0.8	0.5-1%.5% of erythrocytes
Haptoglobin	167	50-220 mg/dL
Coagulation studies/coagulant factors		
Activated partial thromboplastin time	29	25-35 s
Prothrombin time	12	11-13 s
Plasma fibrinogen	250	150-350 mg/dL
D-Dimer	<0.5	<0.5 mg/mL
Anemia evaluation studies		
Iron	65	60-160 mg/dL
Iron-binding capacity, total	352	250-460 mg/dL
Transferrin saturation	18	20%-50%
Ferritin	35	15-200 mg/dL
Folate, serum	15	2.5-20 ng/mL
Vitamin B_{12}, serum	598	200-800 pg/mL

Manual differentiation is within normal limits without schistocytes or abnormality in the white cell line.

Which one of the following is the BEST management strategy for her anemia?

A. Perform a bone marrow biopsy.

B. Simultaneously provide iron supplement and initiate a hypoxia-inducible factor (HIF) stabilizer.

C. Provide iron supplement.

D. Simultaneously provide iron supplement and an ESA.

02. What is the role of the medical director in the case of a hemodialysis patient who frequently has angry verbal outbursts at the nursing staff at the dialysis unit?

A. Transfer the patient to another dialysis and report the patient to the regional dialysis network.

B. Discharge the patient from the dialysis unit.

C. Only provide dialysis when the patient is nonverbally aggressive.

D. Consider psychiatry and/or social work consultation.

03. According to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which one of the following is associated with the BEST outcome in terms of coronary heart disease or nonfatal myocardial infarction and stroke?

A. Calcium channel blocker (CCB)

B. angiotensin converting enzyme inhibitor (ACEi)

C. Thiazide diuretic

D. No difference among CCB, ACEi, and thiazide diuretic

04. A 54-year-old male presents with a history of Liddle syndrome. Which one of the following is MOST consistent with Liddle syndrome?

	Plasma renin	Plasma aldosterone	BP	Treatment
A.	Normal to low	High	Normal	Chlorthalidone
B.	High	High	High	Benazepril
C.	Normal to low	Normal to low	High	Spironolactone
D.	Normal to low	Normal to low	High	Amiloride

05. A 55-year-old female with metastatic ovarian carcinoma is admitted for increasing abdominal distention and reduced urine output despite having relatively normal oral intake over the past week. The patient denies difficulty with starting the urine stream or having any sensation of retention.

The patient has not been taking any medications. Family history and social history are noncontributory.

Physical examination: cachectic female, ill appearing

Vital signs: weight 59 kg, body mass index 22 kg/$m^{2,}$ BP 97/50 mm Hg, mean arterial pressure 66 mm Hg, pulse 98 beats per minute, respiratory rate 20/min, temperature 37.1 °C

Neck: jugular venous pressure 10 cm, no lymphadenopathy

Oropharynx: moist oral mucosa

Lungs: bibasilar crackles

Heart: hyperdynamic heart sounds, no murmurs, rubs, or gallops

Abdomen: poor bowel sounds, markedly distended, tense, moderate diffuse tenderness with palpation

Extremities: 1+ edema up to thighs bilaterally

Skin: warm, no rash

Laboratory studies reveal serum sodium 133 mmol/L, creatinine 3.1 mg/dL (baseline SCr from 2 weeks prior was 1.2 mg/dL), potassium 4.5 mmol/L, albumin 2.0 mg/dL, and lactic acid 4.5 mmol/L. Urine protein to creatinine ratio is 1.1 g/g. Urinalysis is notable for dark yellow urine, specific gravity 1.023, 5 to 10 hyaline casts, and 2 to 5 RBCs/HPF. Hemoglobin is 8.7 g/dL.

ECG: within normal limits

Kidney ultrasound: left kidney 9.8 cm, right kidney 9.5 cm, echogenic kidneys, no hydronephrosis, cysts, or stones

What is the next BEST diagnostic step?

A. Obtain abdominal CT without contrast.

B. Obtain intra-abdominal pressure.

C. Perform furosemide stress test.

D. Obtain postvoid residual volume.

06. Which ONE(s) of the following may contribute to postobstructive diuresis?

A. Continuous saline infusion to match half of urine output

B. Osmotic diuresis due to urea accumulated during the obstructive phase

C. Natriuresis due to sodium and water retention during the obstructive phase

D. All of the above

07. A 78-year-old male with a history of diabetes mellitus, gout, depression, and prostate carcinoma presents to the emergency department with new-onset headaches and weakness.
Medications: empagliflozin, metformin, venlafaxine, abiraterone, losartan, melatonin, and chlorthalidone
Physical examination is notable for BP 180/107 mm Hg and pulse 87 beats per minute. Neurologic examination is nonfocal. The rest of the examination is unremarkable.
The patient denies prior history of hypertension.
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	135	136-145 mmol/L
Potassium	2.9	3.5-5.0 mmol/L
Chloride	93	98-106 mmol/L
Total CO_2 (bicarbonate)	30	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	22	8-20 mg/dL
Creatinine	1.4	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	51	mL/min/1.73 m^2
Glucose (fasting)	156	70-100 mg/dL

Serum chemistry	Patient	Reference range
Albumin	3.2	3.5-5.5 g/dL

Arterial blood gas: pH 7.45, pCO_2 44 mm Hg
Urine sodium: 67 mmol/L, urine chloride 32 mmol/L
Which one of the following is the BEST treatment for this patient's HTN?

A. Angiotensin receptor blocker

B. α-Blocker and β-blocker combination

C. Epithelial sodium channel (ENaC) blocker (amiloride)

D. Eplerenone or low-dose dexamethasone

08. A 51-year-old male with a history of end stage kidney disease due to autosomal dominant polycystic kidney disease, now dialysis dependent, presents for routine care.
Laboratory studies:

Hematology	Patient	Reference range
WBC count	7.8	4-10 × 10^3/mL
Hemoglobin	9.5	Male: 14-17 g/dL
Hematocrit	28.8	Male: 45%-52%
Platelet count	249	150-350 × 10^3/mL
Mean corpuscular volume	80	80-100 fL
Reticulocyte count	0.8	0.5%-1.5% of erythrocytes
Haptoglobin	167	50-220 mg/dL
Coagulation studies/coagulant factors		
Activated partial thromboplastin time	29	25-35 s
Prothrombin time	12	11-13 s

Hematology	Patient	Reference range
Plasma fibrinogen	250	150-350 mg/dL
D-Dimer	<0.5	<0.5 mg/mL
Anemia evaluation studies		
Iron	65	60-160 mg/dL
Iron-binding capacity, total	352	250-460 mg/dL
Transferrin saturation	18	20%-50%
Ferritin	978	15-200 mg/dL
Folate, serum	10	2.5-20 ng/mL
Vitamin B_{12}, serum	598	200-800 pg/mL

Manual differentiation is within normal limits without schistocytes or abnormality in the white cell line.
Which one of the following is the next BEST step?

A. Initiate IV iron supplement for functional iron deficiency.
B. Initiate oral iron supplement and an erythoipoiesis stimulating agent.
C. Initiate oral iron supplement and an hypoxia inducible factor stabilizer.
D. Evaluate for any underlying inflammatory or infectious condition and malnutrition.

09. A 57-year-old male weighing 80 kg with a history of heavy alcohol use, tobacco smoking, and lung adenocarcinoma being treated with chemotherapy including cisplatin is admitted for intractable nausea and vomiting. His only other medication is omeprazole. Laboratory studies:

Hematology	Patient	Reference range
WBC count	5.7	4-10 × 10^3/mL

Hematology	Patient	Reference range
Hemoglobin	11.8	Male: 14-17 g/dL
Hematocrit	35.2	Male: 45%-52%
Platelet count	217	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Reticulocyte count	0.7	0.5%-1.5% of erythrocytes
Haptoglobin	215	50-220 mg/dL
Serum chemistry		
Sodium	133	136-145 mmol/L
Potassium	3.5	3.5-5.0 mmol/L
Chloride	91	98-106 mmol/L
Total CO_2 (bicarbonate)	30	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	13	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL
Glucose (fasting)	72	70-100 mg/dL
Calcium	9.7	9-10.5 mg/dL
Phosphorus	2.9	3-4.5 mg/dL
Magnesium	1.5	1.5-2.4 mg/dL

Urine magnesium 8 mg/dL, creatinine 89 mg/dL
24-hour urine study: creatinine 1,690 mg, magnesium 112 mg (urine magnesium reference range 24-255 mg/d, varies with diet)
Blood gas: pH 7.45, pCO_2 45 mm Hg
What is the MOST likely cause for this patient's hypomagnesemia?

A. Renal wasting

B. Malnutrition

C. Intracellular shift due to metabolic alkalosis

D. Hypovolemia

10. A 47-year-old female presents to the emergency department for new-onset headaches, nausea, dyspnea on exertion, bilateral lower extremity edema, and purpura. Her medical history is notable for relapsing and remitting multiple sclerosis that has been treated with interferon-β for the past 6 years with no known complications.
    Physical examination
    Vital signs: BP of 210/105 mm Hg, pulse 89 beats per minute, respiratory rate 20/min, temperature 37.4 °C
    Neck: jugular venous pressure 10 cm, no lymphadenopathy
    Oropharynx: moist oral mucosa
    Lungs: bibasilar crackles
    Heart: hyperdynamic heart sounds, no murmurs, rubs, or gallops
    Abdomen: flat, normal active bowel sounds, nontender with palpation
    Extremities: 1+ edema up to knees bilaterally
    Skin: notable for a few petechiae on bilateral shins, otherwise within normal limits
    Neurologic: notable for 4/5 strength in the right lower leg, otherwise within normal limits
    Laboratory studies:

Hematology	Patient	Reference range
WBC count	4.2	4-10 × 10^3/mL
Hemoglobin	9.1	Female: 12-16 g/dL
Hematocrit	27.3	Female: 37%-48%
Platelet count	91	150-350 × 10^3/mL
Mean corpuscular	81	80-100 fL

Hematology	Patient	Reference range
volume		
Schistocytes	Few	None
Serum chemistry		
Sodium	132	136-145 mmol/L
Potassium	5.1	3.5-5.0 mmol/L
Chloride	96	98-106 mmol/L
Total CO_2 (bicarbonate)	20	23-28 mmol/L
Anion gap	16	10-14 mmol/L
Blood urea nitrogen	68	8-20 mg/dL
Creatinine	3.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	15	mL/min/1.73 m^2
Glucose (fasting)	75	70-100 mg/dL
Lactate dehydrogenase	475	140-280 U/L
Urinalysis		
Color	Brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.010	1.005-1.025
Glucose	Negative	≤130 mg/dL
Ketones	Negative	Negative
Nitrites	Negative	Negative

Hematology	Patient	Reference range
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Large	Negative
Protein	1+	Negative
Red blood cells (RBCs)	5-10 dysmorphic	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	Granular casts	None
Bacteria	None	None

Serologies: complement C3 67 mg/dL (normal 90-180 mg/dL), C4 within normal limit

All other serologies including antinuclear antibody, cryoglobulins, ANCA, antiphospholipid antibodies, acute hepatitis panel, HIV, CMV, EBV, and parvovirus B19 were within normal limits.

Coagulation studies: normal prothrombin time and activated prothrombin time

ADAMTS13 (**A** **D**isintegrin **A**nd **M**etalloproteinase with a **T**hrombospondin type 1 motif, member **13**) activity 60%

Urine protein to creatinine ratio 1.5 g/g

Kidney ultrasound: right kidney 10 cm, left kidney 11.2 cm, increased cortical echogenicity bilaterally, no hydronephrosis, cyst, or mass

What is the next BEST step?

A. Stop interferon therapy.

B. Perform emergent plasma exchange (PLEX).

C. Obtain β-human chorionic gonadotropin level.

D. Evaluate for underlying cause of disseminated intravascular coagulopathy (DIC).

11. A 57-year-old female who is morbidly obese with hypertension, hyperlipidemia, and chronic obstructive pulmonary disorder presents with dyspnea on exertion and is found to have acute decompensated heart failure with severe volume overload.
The patient is placed on furosemide and afterload reduction with losartan. Over the next 3 days, the patient's oxygenation improves, but she is noted to become less arousable.
Brain CT is negative for any acute bleed.
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	135	136-145 mmol/L
Potassium	3.3	3.5-5.0 mmol/L
Chloride	85	98-106 mmol/L
Total CO_2 (bicarbonate)	38	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	28	8-20 mg/dL
Creatinine	1.5	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	40	mL/min/1.73 m^2
Glucose (fasting)	112	70-100 mg/dL
Albumin	3.5	3.5-5.5 g/dL

Arterial blood gas: pH 7.26, pCO_2 69 mm Hg
Despite having a net negative fluid balance of 8.5 L over the past 3 hospital days, the patient's physical examination is still notable

for significant bilateral crackles up 1/3 in both lung fields and significant peripheral edema.
Which one of the following is the next BEST step?

A. Add thiazide diuretic.
B. Replace fluid loss with normal saline.
C. Replace fluid loss with lactated Ringer solution.
D. Provide noninvasive positive pressure support and add acetazolamide.

12. A 55-year-old female with end stage kidney disease due to type 2 diabetes mellitus, requiring kidney replacement therapy, hypertension coronary artery disease requiring two drug-eluting stents, anemia of chronic disease, and breast cancer being treated by oncology presents for routine follow-up with her primary care provider. Her systolic blood pressure has been ranging from 170 to 200 mm Hg over the past 3 months. Her provider asks for your advice on initiating an ESA for her hemoglobin of 10.1 g/dL.
Which one of the following is the BEST advice?

A. She can be initiated on either an erythropoesis stimulating agent or hypoxia inducible factor stabilizer once her BP is better controlled.
B. She is at increased risk for thrombotic complications and cardiovascular events and possibly increased mortality risk with the use of ESA or HIF stabilizer.
C. She can be initiated on either an ESA or an HIF stabilizer.
D. She can be initiated on an ESA, but not an HIF stabilizer.

13. A 37-year-old male with bilateral renal cell carcinoma (RCC) presents for evaluation of his chronic kidney disease stage G3aA1. Routine evaluation reveals blood pressure of 157/89 mm Hg and pulse of 78 beats per minute. The patient endorses that he does have intermittent hypertensive episodes that were attributed to anxiety. He denies any family history of hypertension.
What is the next BEST step?

A. Obtain an electrocardiogram or two-dimensional echocardiogram.

B. Obtain 24-hour ambulatory BP measurements.

C. Obtain plasma-free metanephrines.

D. Obtain thyroid function test.

14. A 48-year-old female with no past medical history presents with fatigue, generalized weakness, poor concentration and memory, and weight gain of 20 lb over the past 6 months. Physical examination is notable for elevated blood pressure of 170/110 mm Hg, pulse 87/min, and central obesity.
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	140	136-145 mmol/L
Potassium	3.2	3.5-5.0 mmol/L
Chloride	101	98-106 mmol/L
Total CO_2 (bicarbonate)	28	23-28 mmol/L
Blood urea nitrogen	9	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL
Glucose (fasting)	145	70-100 mg/dL
Calcium	9.4	9-10.5 mg/dL
Phosphorus	4.2	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL

Urinalysis is bland without proteinuria, glucose, or cells.
What is the BEST diagnostic test?

A. Plasma renin activity and aldosterone

B. Thyroid function

C. Morning cortisol

D. 24-hour urine creatinine and free cortisol excretion and 1 mg overnight dexamethasone suppression test (DST)

15. A 66-year-old male with no past medical history presents with total body pain for the past 2 months. Review of systems is otherwise negative. Medication includes ibuprofen 800 mg tid for the past month.
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	7.2	4-10 × 10^3/mL
Hemoglobin	8.6	Male: 14-17 g/dL
Hematocrit	25.8	Male: 45%-52%
Platelet count	178	150-350 × 10^3/mL
Mean corpuscular volume	81	80-100 fL
Schistocytes	None	None
Serum chemistry		
Sodium	132	136-145 mmol/L
Potassium	5.1	3.5-5.0 mmol/L
Chloride	107	98-106 mmol/L
Total CO_2 (bicarbonate)	20	23-28 mmol/L
Anion gap	5	10-14 mmol/L
Blood urea nitrogen	68	8-20 mg/dL
Creatinine	6.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	8	mL/min/1.73 m^2
Glucose (fasting)	95	70-100 mg/dL

Hematology Urinalysis	Patient	Reference range
Color	Dark yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.020	1.005-1.025
Glucose	Trace	Negative
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Large	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	None	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	None	None

Urine protein to creatinine ratio 2.7 g/g
Urine albumin to creatinine ratio 125 mg/g
Serum κ light chains 7,250 mg/L (reference range: 3.3-19.4 mg/L), λ light chains 67 mg/L (reference range: 5.7-26.3 mg/L)
Which one of the following is the MOST likely diagnosis for his kidney injury?

A. AL amyloidosis
B. Acute interstitial nephritis (AIN)
C. C3 glomerulonephropathy
D. Myeloma kidney

16. All of the following have been linked to the use of levamisole-laced cocaine EXCEPT:
A. ANCA vasculitis
B. Thrombotic microangiopathy (TMA)
C. Immune complex glomerulonephritis
D. Renal infarction

17. A 72-year-old male with a history of granulomatous polyangiitis associated with anti-myeloperoxidase (anti-MPO) antibody and renal involvement with maximum serum creatinine (SCr) reaching 3.2 mg/dL now presents for routine follow-up at month sixth following rituximab (RTX) induction. His maintenance therapy is RTX. His current laboratory studies: SCr is 1.8 mg/dL, urine protein to creatinine ratio 0.4 g/g, and ANCA titer has remained at a low level (anti-MPO titer ranging from 3.5 to 5.0 IU/mL) since induction.
Which ONE of the following factors portends greater relapse risk of ANCA-associated glomerulonephritis in this patient?
A. Anti-MPO antibody positivity
B. ANCA positivity at the end of induction
C. Serum creatinine greater than 3 mg/dL at presentation
D. Older age

18. A 78-year-old male with a history of obesity class 1, type 2 diabetes mellitus, and chronic kidney disease stage G3A3 from diabetic kidney disease is admitted for *S. aureus* pneumonia and septic shock requiring intermittent hemodialysis support. Despite daily dialysis support, his chemistry panel reveals significant electrolyte disturbances.

Hematology	Day 1	Day 2	Day 3	Reference range
WBC count	7.8	8.1	9.7	4-10 × 10^3/mL
Hemoglobin	9.5	8.9	9.2	Male: 14-17 g/dL
Hematocrit	28.8	26.9	28.1	Male: 45%-52%
Platelet count	249	267	281	150-350 × 10^3/mL
Mean corpuscular volume	80	81	81	80-100 fL
Reticulocyte count	0.7	0.5	0.4	0.5%-1.5% of erythrocytes
Haptoglobin	167	178	159	50-220 mg/dL
Serum chemistry				
Sodium	133	132	132	136-145 mmol/L
Potassium	5.8	5.9	6.1	3.5-5.0 mmol/L
Chloride	91	90	91	98-106 mmol/L
Total CO_2 (bicarbonate)	22	20	18	23-28 mmol/L
Anion gap	20	22	23	10-14 mmol/L
Blood urea nitrogen	110	80	55	8-20 mg/dL
Creatinine	10.5	7.5	5.1	0.7-1.3 mg/dL
Glucose (fasting)	99	89	106	70-100 mg/dL
Total calcium	9.1	8.8	7.2	8.5-10.2 mg/dL
Phosphorus	10.1	12.4	11.9	2.8-4.5 mg/dL

Which one of the following can BEST explain his persistent abnormal electrolyte findings?

A. Hemolysis

B. Rhabdomyolysis or tissue necrosis

C. Inadequate dialysis in patient with hypercatabolic state

D. Ogilvie syndrome associated with acute stress state

19. A 55-year-old female is admitted to the hospital for acute decompensated heart failure, with an ejection fraction of 20% to 25%. You are consulted for the management of hyponatremia.
Physical examination: Patient appears to be in distress with breathing difficulty.
Vital signs: weight 50 kg, BP 102/57 mm Hg, pulse 99 beats per minute, respiratory rate 23/min, temperature 36.7 °C
Head and neck: moist oral mucosa, jugular venous distention up to jaw
Lungs: crackles up half of lungs bilaterally
Heart: regular S_1, S_2, $+S_3/S_4$, 2/6 systolic murmur left upper sternal border
Extremities: 2+ edema up to knees bilaterally
Neurologic: nonfocal
Laboratory studies:

Metabolic profile on admission	Patient	Reference range
Sodium	125	136-145 mmol/L
Potassium	3.5	3.5-5.0 mmol/L
Chloride	81	98-106 mmol/L
Total CO_2 (bicarbonate)	32	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	17	8-20 mg/dL
Creatinine	1.4	0.7-1.3 mg/dL
Glucose (fasting)	87	70-100 mg/dL
Calcium	9.3	9-10.5 mg/dL

Metabolic profile on admission	Patient	Reference range
Phosphorus	4.1	3-4.5 mg/dL
Magnesium	2.1	1.5-2.4 mg/dL
Plasma osmolarity	262	275-295 mOsm/L
Lactate dehydrogenase	54	60-100 U/L

Urine studies: osmolality 352 mOsm/kg, sodium 70 mmol/L, potassium 30 mmol/L
The patient is placed on continuous bumetanide infusion and 1 L free water restriction daily.
Urine output over the past 24 hours is 2 L.
Which of the following is the MOST correct statement?

A. Tolvaptan can improve fluid removal, hyponatremia, and long-term survival.
B. Free water restriction of 750 mL/d will improve current hyponatremia.
C. Acetazolamide can help improve metabolic alkalosis and hypokalemia.
D. Current free water restriction will not be effective in improving the patient's hyponatremia.

20. Which one of the following complications of chronic kidney disease is NOT associated with increased mortality risk?

A. Calcific uremic arteriolopathy
B. Restless leg syndrome (RLS)
C. Absence of nocturnal BP dipping
D. None of the above

21. A 58-year-old male presents with acute onset severe back pain. Blood pressure at intake is 210/120 mm Hg, pulse 94/min. A STAT CT angiography is consistent with an acute dissecting abdominal aortic aneurysm.
What is the next BEST step?

A. Initiate a β-blocker drip (eg, esmolol, labetalol, metoprolol) to reduce pulse to below 60/min with or without a second vasodilator drip (eg, nitroprusside, clevidipine, or nicardipine) as necessary to reduce systolic blood pressure (SBP) to 100 to 120 mm Hg within 20 minutes.

B. Initiate a vasodilator drip (eg, nitroprusside, clevidipine, or nicardipine) to reduce his SBP to below 120 mm Hg within 20 minutes.

C. Initiate a vasodilator drip (eg, nitroprusside, clevidipine, or nicardipine) to reduce his SBP by 25% within 24 hours.

D. Initiate hydralazine drip to reduce his SBP by 25% within 24 hours.

22. A 45-year-old female with newly diagnosed Guillain-Barré syndrome is admitted to the neurology service for evaluation and management. The patient has no other medical history. Review of systems is notable for progressive muscle weakness of both arms and legs and inability to walk more than 10 ft.

Medications: omeprazole 20 mg bid, intravenous immunoglobulin (IVIG) (formulated with glycine, osmolality 258 mOsm/kg) 0.4 g/kg/d, status post 5 days of treatment, diphenhydramine 25 mg and acetaminophen 650 mg to be given with IVIG treatments, 5% dextrose (D5) half-normal saline at 75 mL/h as maintenance fluid

Physical examination: Patient appears anxious but in no acute distress.

Vital signs: weight 70 kg, BP 112/67 mm Hg, pulse 91 beats per minute, respiratory rate 18/min, temperature 37.6 °C

Head and neck: within normal limits; moist oral mucosa

Lungs: clear to auscultation bilaterally

Heart: regular, normal S_1, S_2, no murmurs, gallops, rubs

Extremities: no clubbing, cyanosis, or edema

Neurologic: 2 to 3 out of 4 strength bilateral upper and lower extremities, sensory intact, deep tendon reflexes 1+ symmetric throughout

Laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	129 (135 on admission)	136-145 mmol/L
Potassium	4.2	3.5-5.0 mmol/L
Chloride	96	98-106 mmol/L
Total CO_2 (bicarbonate)	23	23-28 mmol/L
Anion gap	5	10-14 mmol/L
Blood urea nitrogen	16	8-20 mg/dL
Creatinine	1.0	0.7-1.3 mg/dL
Glucose (fasting)	112	70-100 mg/dL
Calcium	9.5	9-10.5 mg/dL
Phosphorus	4.1	3-4.5 mg/dL
Magnesium	2.4	1.5-2.4 mg/dL
Plasma osmolarity	284	275-295 mOsm/L
Lactate dehydrogenase	112	60-100 U/L

Urine studies: osmolality 273 mOsm/kg, sodium 43 mmol/L, potassium 20 mmol/L

What is the MOST likely diagnosis for this patient's hyponatremia?

A. Glycine-induced hyponatremia

B. Psychogenic polydipsia

C. Syndrome of inappropriate release of antidiuretic hormone (SIADH)

D. Pseudohyponatremia

23. A 33-year-old female with type 1 diabetes mellitus presents with nausea, vomiting, and poor oral intake for 2 days following a cruise to Alaska. Review of systems is otherwise negative. Physical examination: Patient appears fatigued, acutely ill.

Vital signs: weight 65 kg, BP 122/67 mm Hg, pulse 83 beats per minute, respiratory rate 18/min, temperature 37.6 °C. There is no orthostatic hypotension.
Head and neck: within normal limits; dry oral mucosa
Lungs: clear to auscultation
Heart: tachycardic but regular, normal S_1, S_2, no murmurs, gallops, rubs
Extremities: no clubbing, cyanosis, or edema
Neurologic: nonfocal
Laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	140	136-145 mmol/L
Potassium	3.7	3.5-5.0 mmol/L
Chloride	99	98-106 mmol/L
Total CO_2 (bicarbonate)	27	23-28 mmol/L
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	35	8-20 mg/dL
Creatinine	1.5	0.7-1.3 mg/dL
Glucose (fasting)	400	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	4.5	3-4.5 mg/dL
Magnesium	2.2	1.5-2.4 mg/dL
Plasma osmolarity	335	275-295 mOsm/L
Lactate dehydrogenase	112	60-100 U/L

Which one of the following is the BEST treatment option?

A. Start 150 mL/h of 5% dextrose water over the next 24 hours.

B. Administer 500 mL of normal saline as a bolus, followed by 75 mL/h × 24 h of normal saline.

C. Administer 500 mL of lactated Ringer as a bolus, followed by 75 mL/h × 24 h of normal saline.

D. Bolus 500 mL of half-normal saline, followed by 100 mL/h × 24 h of half-normal saline for the next 24 hours.

24. A 20-year-old female is brought to the emergency department by her friends for a witnessed generalized tonic-clonic seizure following a night partying. She reportedly has no known medical history.

Physical examination is notable for a postictal state. Vital signs notable for tachycardia with pulse ranging between 90 and 100 beats per minute, normal respiratory rate of 18/min, BP of 121/74, temperature of 37.8 °C. Physical examination is otherwise within normal limits.

Laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	117	136-145 mmol/L
Potassium	5.2	3.5-5.0 mmol/L
Chloride	86	98-106 mmol/L
Total CO_2 (bicarbonate)	17	23-28 mmol/L
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	12	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	83	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	5.4	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL

Metabolic profile	Patient	Reference range
Albumin	4.2	3.5-5.5 g/dL
Creatinine phosphokinase	1,237	26-140 U/L

Urine studies: osmolality 267 mOsm/kg, sodium 57 mmol/L, potassium 173 mmol/L
Urine drug screen is positive for amphetamine.
Serum ethanol, acetaminophen, and salicylate are negative.
Which one(s) of the following recreational drugs have MOST likely contributed to the laboratory studies above?

A. 3,4-methylenedioxymethamphetamine (MDMA) a.k.a. ecstasy

B. Cocaine

C. Cannabis and synthetic cannabinoids

D. Both A and C

25. A 69-year-old female with newly diagnosed cirrhosis, diabetes mellitus, and hypertension is admitted for altered mental status due to presumed hepatic encephalopathy. Routine evaluation included an abdominal and pelvic CT with intravenous contrast done for abdominal pain. Three days following admission, you are asked to evaluate for new-onset acute kidney injury, with a creatinine increase from 1.2 mg/dL on admission to 1.8 mg/dL.
Medications: lactulose, multivitamin, folate, thiamine, amlodipine 10 mg daily, insulin
Physical examination
Vital signs: BP of 111/65 mm Hg, pulse 79 beats per minute, respiratory rate 16/min, temperature 36.7 °C
Neck: no jugular venous distention, no lymphadenopathy
Oropharynx: dry oral mucosa
Lungs: bibasilar crackles
Heart: hyperdynamic heart sounds, no murmurs, rubs, or gallops
Abdomen: mildly distended, normal active bowel sounds, soft, nontender
Extremities: no edema

Skin: notable for a few petechiae on bilateral shins, otherwise within normal limits
Neurologic: notable for 4/5 strength in the right lower leg, otherwise within normal limits
Laboratory studies:

Hematology	Patient	Reference range
White blood cell count	5.2	4-10 × 10^3/mL
Hemoglobin	8.8	Female: 12-16 g/dL
Hematocrit	26.5	Female: 37%-48%
Platelet count	168	150-350 × 10^3/mL
Mean corpuscular volume	95	80-100 fL
Schistocytes	None	None
Serum chemistry		
Sodium	129	136-145 mmol/L
Potassium	5.9	3.5-5.0 mmol/L
Chloride	96	98-106 mmol/L
Total CO_2 (bicarbonate)	23	23-28 mmol/L
Anion gap	10	10-14 mmol/L
Blood urea nitrogen	33	8-20 mg/dL
Creatinine	2.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	19	mL/min/1.73 m^2
Glucose (fasting)	432	70-100 mg/dL
Liver function tests		
Total protein	5.3	6.0-7.8 g/dL

Hematology	Patient	Reference range
Albumin	2.1	3.5-5.5 g/dL
Alanine aminotransferase (ALT)	118	0-35 U/L
Aspartate aminotransferase (AST)	187	0-35 U/L
Alkaline phosphatase	111	36-92 U/L
Total bilirubin	6.2	0.3-1.2 mg/dL
Direct bilirubin	4.8	0-0.3 mg/dL
Coagulation studies		
Activated partial thromboplastin time	28	25-35 s
Prothrombin time	14	11-13 s
Plasma fibrinogen	189	150-350 mg/dL
Urinalysis		
Color	Brown	Yellow
Clarity/turbidity	Clear	Clear
pH	5.5	4.5-8.0
Specific gravity	1.012	1.005-1.025
Glucose	Negative	Negative
Ketones	1+	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Large	Negative

Hematology	Patient	Reference range
Urobilirubin	2.5	0.5-1.0 mg/dL
Blood	Large	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	None	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	None	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	Few granular casts	None

What is the BEST management strategy?

A. Administer lactated Ringer solution.

B. Administer 25% albumin at 1 g/kg/d.

C. Administer insulin and normal saline.

D. Administer terlipressin.

26. A 57-year-old female with a history of chronic kidney disease (CKD) stage G5A2 of unknown etiology and HTN presents for a routine follow-up of her chronic kidney disease (CKD). She has not noticed any change in her energy over the past couple of months but mentions that she switched her job working as a salesclerk at a department store to being a telemarketer so she can work from home due to a sprained ankle 3 months ago. Review of systems is notable for 3 kg weight loss due to depression and poor appetite. She otherwise denies any short of breath, chest pain, worsening of pedal edema, or change in urine output. She does not routinely exercise.
Medications: losartan, amlodipine, furosemide, atorvastatin, sevelamer carbonate, calcitriol, sodium bicarbonate
Physical examination is only notable for 1+ bilateral ankle edema.

Laboratory studies over the past 6 months

Hematology	6 mo ago	3 mo ago	Today	Reference range
WBC count	7.8	8.1	6.7	4-10 × 10^3/mL
Hemoglobin	10.5	10.1	9.9	Female: 12-16 g/dL
Hematocrit	32.7	30.2	31.1	Female: 37%-48%
Platelet count	249	267	281	150-350 × 10^3/mL
Mean corpuscular volume	80	81	81	80-100 fL
Reticulocyte count	0.6	0.5	0.4	0.5%-1.5% of erythrocytes
Haptoglobin	167	178	159	50-220 mg/dL
Serum chemistry				
Sodium	133	132	132	136-145 mmol/L
Potassium	4.5	4.4	4.5	3.5-5.0 mmol/L
Chloride	91	90	91	98-106 mmol/L
Total CO_2 (bicarbonate)	22	20	18	23-28 mmol/L
Anion gap	20	22	23	10-14 mmol/L
Blood urea nitrogen	54	67	80	8-20 mg/dL
eGFR	15	13	11	>60 mL/min/1.73 m^2
Glucose (fasting)	99	89	78	70-100 mg/dL
Total calcium	9.1	8.8	8.2	8.5-10.2 mg/dL
Phosphorus	5.5	5.3	5.9	2.8-4.5 mg/dL

Hematology	6 mo ago	3 mo ago	Today	Reference range
Albumin	3.4	3.2	2.9	3.5-5.5 g/dL

What is the next BEST step?

A. Provide nutritional support.

B. Initiate kidney replacement therapy.

C. Increase current dose of sodium bicarbonate.

D. Add calcium carbonate.

27. Anticoagulation therapy is NOT recommended for which one of the following conditions?

A. Deep vein thrombosis (DVT) in minimal change disease

B. Atrial fibrillation in patients with end stage kidney disease

C. Antiphospholipid syndrome (APS) in systemic lupus erythematosus (SLE)

D. Atheroembolic disease

28. A 47-year-old male weighing 80 kg with a history of anuric end stage kidney disease due to anti-glomerular basement membrane disease, requiring chronic hemodialysis thrice weekly for 3 years, is admitted for evaluation of an upper gastrointestinal bleed. The nephrology service is consulted to provide continuing dialysis support while the patient remains hospitalized. Physical examination is notable for a euvolemic patient. The patient's daily net fluid balance ranges between 1.5 and 2.0 L/d.
Laboratory studies:

Serum chemistry	Predialysis	Postdialysis	Reference range
Sodium	133	139	136-145 mmol/L
Potassium	4.5	4.2	3.5-5.0 mmol/L
Chloride	91	101	98-106 mmol/L
Total CO_2 (bicarbonate)	22	24	23-28 mmol/L

Serum chemistry	Predialysis	Postdialysis	Reference range
Anion gap	20	14	10-14 mmol/L
Blood urea nitrogen	70	35	8-20 mg/dL
Creatinine	5.4	3.4	0.7-1.3 mg/dL
Glucose (fasting)	99	89	70-100 mg/dL
Total calcium	9.1		8.5-10.2 mg/dL
Phosphorus	5.5		2.8-4.5 mg/dL
Albumin	3.4		3.5-5.5 g/dL

3.2 L of fluid is removed with dialysis. Range fluid removal is 3 to 4L at each session.

Which one of the following is a CORRECT statement regarding the dialysis therapy for this patient?

A. Solute clearance and ultrafiltration (UF) rate are reasonable.

B. Solute clearance needs to be improved. UF rate is reasonable.

C. Solute clearance needs to be improved. UF rate, thus daily fluid intake, needs to be reduced.

D. Solute clearance is reasonable. UF rate, thus net fluid balanced, needs to be reduced.

29. Which ONE of the following conditions can present with both obstructive uropathy and interstitial nephritis?

A. IgG4-related disease (IgG4-RD)

B. Hyperoxaluria

C. Renal tuberculosis

D. All of the above

30. The following set of laboratory results was not labeled with patient's name in a busy emergency department.

Serum chemistry	Patient	Reference range
Sodium	140	136-145 mmol/L
Potassium	3.3	3.5-5.0 mmol/L
Chloride	85	98-106 mmol/L
Total CO_2 (bicarbonate)	24	23-28 mmol/L
Anion gap	21	10-14 mmol/L
Blood urea nitrogen	20	8-20 mg/dL
Creatinine	1.2	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	40	mL/min/1.73 m^2
Glucose (fasting)	112	70-100 mg/dL
Albumin	3.5	3.5-5.5 g/dL

Arterial blood gas: pH 7.40, pCO_2 41 mm Hg

The laboratory set above MOST likely belongs to which one of the following patients?

A. A 27-year-old female who presents for an anxiety attack

B. A 67-year-old male with daily 1,000 mg calcium carbonate ingestion who presents with diarrhea

C. A 47-year-old female who presents with intractable nausea and vomiting and sepsis

D. A 33-year-old male who presents with a head laceration

31. A 33-year-old Hispanic female with a history of lupus nephritis (LN) classes III and V, in remission for 18 months, presents with an acute rise in serum creatinine at her routine 3-month follow-up. She endorses adherence to all her medications. Medications include mycophenolate mofetil, hydroxychloroquine, and occasional ibuprofen for menstrual cramps.
Laboratory studies:

	3 mo ago	Now
SCr	0.8 mg/dL	1.7 mg/dL
C3 (55-120 mg/dL)	65	87
C4 (16-48 mg/dL)	22	31
CH50 (37-55 U/mL)	42	42
Anti–double-stranded DNA	None detected	None detected
Urine protein to creatinine ratio	0.2 g/g	1.4 g/g creatinine
Urine albumin to creatinine ratio	25 mg/g	35 mg/g creatinine

Urinalysis is bland with approximately 100 mg/dL protein and without cells or casts.
Kidney ultrasound is negative for any structural abnormality.
Bladder scan is negative for any postvoid residual volume.
Which one of the following is the next BEST step?

A. Switch mycophenolate mofetil to cyclophosphamide.
B. Continue the current regimen, discontinue ibuprofen, and monitor closely.
C. Switch mycophenolate mofetil to rituximab.
D. Add voclosporin to the current regimen.

32. Which one of the following statements is CORRECT?

A. Antibodies directed against HLA class I will only result in a positive crossmatch with T cells.
B. Antibodies directed against HLA class II will only result in a positive crossmatch with T cells.
C. Antibodies directed against HLA class II can result in a positive crossmatch with both B and T cells.
D. Antibodies directed against HLA class I can result in a positive crossmatch with both B and T cells.

33. A 25-year-old male was brought by family to the emergency department due to altered mental status and new-onset seizure. Initial vital signs and laboratory evaluation showed temperature of 40 °C, BP 180/90 mm Hg, pulse 110 beats per minute, and respiratory rate 20/min. Sodium 110 mmol/L, chloride 78 mmol/L, potassium 6.5 mmol/L, bicarbonate 16 mmol/dL, blood urea nitrogen 30 mg/dL, creatinine 5.1 mg/dL, creatinine phosphokinase 10,500 U/L, urinalysis showed 3+ blood, 0 to 2 red blood cells per high power field.
Which one of the following is the MOST likely cause of this patient's clinical presentation?

A. Levamisole-laced cocaine use

B. Ingestion of ecstasy

C. Ingestion of bath salts

D. Intravenous heroin use

34. A 31-year-old male with type 1 diabetes mellitus, known to be noncompliant with taking his medications, presents with lethargy and the following laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	127	136-145 mmol/L
Potassium	3.0	3.5-5.0 mmol/L
Chloride	94	98-106 mmol/L
Total CO_2 (bicarbonate)	12	23-28 mmol/L
Anion gap	21	10-14 mmol/L
Blood urea nitrogen	37	8-20 mg/dL
Creatinine	1.5	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	63	mL/min/1.73 m^2
Glucose (fasting)	578	70-100 mg/dL

Serum chemistry	Patient	Reference range
Albumin	3.5	3.5-5.5 g/dL

Serum ketones: moderate
Arterial blood gas: pH 7.22, pCO_2 30 mm Hg
Which one of the following is the next BEST step?

A. Initiate insulin drip.

B. Replace potassium.

C. Intubate for mechanical ventilation.

D. Infuse sodium bicarbonate (150 mmol/L) at 200 mL/h.

35. A 65-year-old male weighing 78 kg is referred to your ambulatory clinic for evaluation of recurrent kidney stones. His 24-hour urine metabolic profile is as follows:

24-h urine metabolic profile	Patient	Reference range
Creatinine	1,560	Male: 20-25 mg/kg/24 h
Volume	1,270	L (variable)
pH	5.5	Variable
Calcium	270	Male: <250 mg/24 h
Uric acid	856	Male: <800 mg/24 h
Oxalate	39	<40 mg/24 h
Citrate	250	≥450 mg/24 h
Phosphorus	1,879	Male: 390-1,425 mg/24 h
Sodium	354	mmol (variable)

Which one of the following is the MOST likely reason for this patient's recurrent stones?

A. Primary hyperoxaluria

B. Poor dietary habit (eg, fast foods)

C. Abnormal anatomy of the collecting system

D. Familial disposition

36. A 55-year-old male with newly diagnosed ANCA-associated GN and coexisting high titer anti-GBM asks for your opinion regarding his prognosis regarding the significance of coexisting serologies of ANCA and anti-glomerular basement membrane antibody (anti-GBM). His serum creatinine is currently 2.1 mg/dL. He has no upper respiratory signs or symptoms. Which one of the following is a CORRECT statement?

A. He does not need plasmapheresis given his relatively good kidney function.

B. The course of his ANCA vasculitis depends on his anti-GBM titer.

C. Similar to the treatment of anti-GBM disease, he does not need maintenance immunosuppressive therapy.

D. When ANCA and anti-GBM antibodies coexist, the disease course is similar to that seen in anti-GBM disease in early disease, but the relapse pattern is similar to ANCA disease.

37. A 61-year-old female with a history of hypertension and end stage kidney disease due to lupus nephritis, hemodialysis dependent since the last 6 months, is a new patient who is just transferred to your dialysis unit. Since the initiation of HD, she has been feeling and eating better. She has also joined a Zumba class with her neighbor and has worked out with weights at least 5 times a week. Based on her previous dialysis unit, her recorded dry weight 1 month ago was 60 kg. Entry weight to your dialysis unit is 65 kg.

Medications: losartan, omeprazole, sevelamer carbonate, cholecalciferol, iron supplement

Physical examination is negative for lung crackles or pedal edema. She has no evidence of serologic or extrarenal manifestations of any lupus flare.

Initial dialysis order is placed to remove 2 to 3 L as safely tolerated over 3 hours. Dialysate with 140 mmol/L sodium,

potassium 3 mmol/L, and calcium 2.25 mEq/L is used. The dialysate temperature is set at 1 °C less than the patient's body temperature. Halfway through the treatment, when only 800 mL of fluid had been removed, the patient experiences hypotension associated with tachycardia and cramping but without chest pain, short of breath, fevers, chills, headaches, nausea, or vomiting.
Which one of the following is the MOST likely reason for her hypotension?

A. Increased dry weight

B. Dialysate temperature being too warm

C. Angina equivalent

D. Ultrafiltration rate being too fast

38. A 72-year-old female with a history of type 2 diabetes mellitus, hypertension hyperlipidemia, and chronic kidney disease stage G3aA3 (baseline eGFR 50-55 mL/min/1.73 m^2) is brought from the nursing home for failure to thrive. Medications include insulin, hydralazine, carvedilol, chlorthalidone, empagliflozin, and diphenhydramine as needed for sleep. The patient has a history of angioedema with angiotenism converting enzyme inhibitors.
Physical examination
Vital signs: BP of 161/95 mm Hg, pulse 99 beats per minute, respiratory rate 16/min, temperature 37.4 °C
Neck: jugular venous pressure 8 cm, no lymphadenopathy
Oropharynx: dry oral mucosa
Lungs: bibasilar crackles
Heart: hyperdynamic heart sounds, no murmurs, rubs, or gallops
Abdomen: mildly distended, normal active bowel sounds, moderate tenderness with palpation in the lower abdomen
Extremities: trace ankle edema bilaterally
Laboratory studies:

Hematology	Patient	Reference range
WBC count	6.2	4-10 × 10^3/mL
Hemoglobin	11.8	Female: 12-16 g/dL

Hematology	Patient	Reference range
Hematocrit	35.4	Female: 37%-48%
Platelet count	368	150-350 × 10^3/mL
Mean corpuscular volume	92	80-100 fL
Serum chemistry		
Sodium	132	136-145 mmol/L
Potassium	6.5	3.5-5.0 mmol/L
Chloride	102	98-106 mmol/L
Total CO_2 (bicarbonate)	12	23-28 mmol/L
Anion gap	18	10-14 mmol/L
Blood urea nitrogen	45	8-20 mg/dL
Creatinine	2.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	18	mL/min/1.73 m^2
Glucose (fasting)	188	70-100 mg/dL
Total protein	5.3	6.0-7.8 g/dL
Albumin	2.7	3.5-5.5 g/dL
Coagulation studies		
Activated partial thromboplastin time	26	25-35 s
Prothrombin time	12	11-13 s
Urinalysis		
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear

Hematology	Patient	Reference range
pH	5.5	4.5-8.0
Specific gravity	1.013	1.005-1.025
Glucose	1+	Negative
Ketones	1+	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Moderate	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Small	Negative
Protein	>300 mg/dL	Negative
Red blood cells (RBCs)	0-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	10-15	≤2-5 WBCs/HPF
Squamous epithelial cells	Many	<15-20 squamous epithelial cells/HPF
Bacteria	Few	None

Which one of the following is the MOST likely cause for her acute kidney injury (AKI)?

A. Acute interstitial nephritis (AIN)

B. Neurogenic bladder

C. Pyelonephritis

D. Diabetic kidney disease

39. Which one of the following clinical manifestations is NOT suggestive of downstream stenosis of an arteriovenous (AV) vascular access (eg, AV fistula)?

A. Ipsilateral hand edema

B. Persistent hyperkalemia

C. Facial edema

D. Increased venous access pressure

40. You are called by the urgent care physician who asks for your opinion regarding invasive therapy for bilateral renal artery stenosis in a 57-year-old male with a history of type 2 diabetes mellitus and medically controlled hypertension (HTN).
Which ONE of the following precludes invasive therapy for renal artery stenosis (eg, bilateral renal angioplasty)?

A. Kidney size less than 8.5 cm bilaterally

B. Poorly controlled HTN despite being on appropriate therapy and with rapidly deteriorating kidney function

C. Serum creatinine greater than 2 mg/dL

D. Renal arterial resistive index less than 0.7

41. A 55-year-old male with a history of hypertension presents with headaches, nausea, and blurry vision. Initial evaluation reveals blood pressure of 200/110 mm Hg, acute kidney injury, and microscopic hematuria. Fundoscopic examination shows cotton wool spots, hard exudates, flame hemorrhages, and papilledema. Physical examination is otherwise within acceptable limits. There are no vascular bruits or abdominal pulsatile mass. Neurologic examination is nonfocal. Brain CT is negative for any evidence of stroke or acute bleed.
Which one of the following is the BEST management strategy?

A. SBP should be lowered to target of 100 to 120 mm Hg *within 20 minutes*.

B. Reduce mean arterial pressure by 10% to 20% in the first hour, then by an additional 5% to 15% over the next 23 hours, for a total 24-hour BP reduction of less than 25%.

C. Acute lowering of systolic blood pressure to 140 to 160 mm Hg is suggested.

D. Reduce mean arterial pressure by 25% within 8 hours.

42. Which one of the following regarding post-transplantation malignancies is CORRECT?

A. Skin cancer is the most common de novo post-transplant malignancy in the adult transplant population.

B. mTOR inhibitor use is effective in primary, but not secondary, skin cancer prevention.

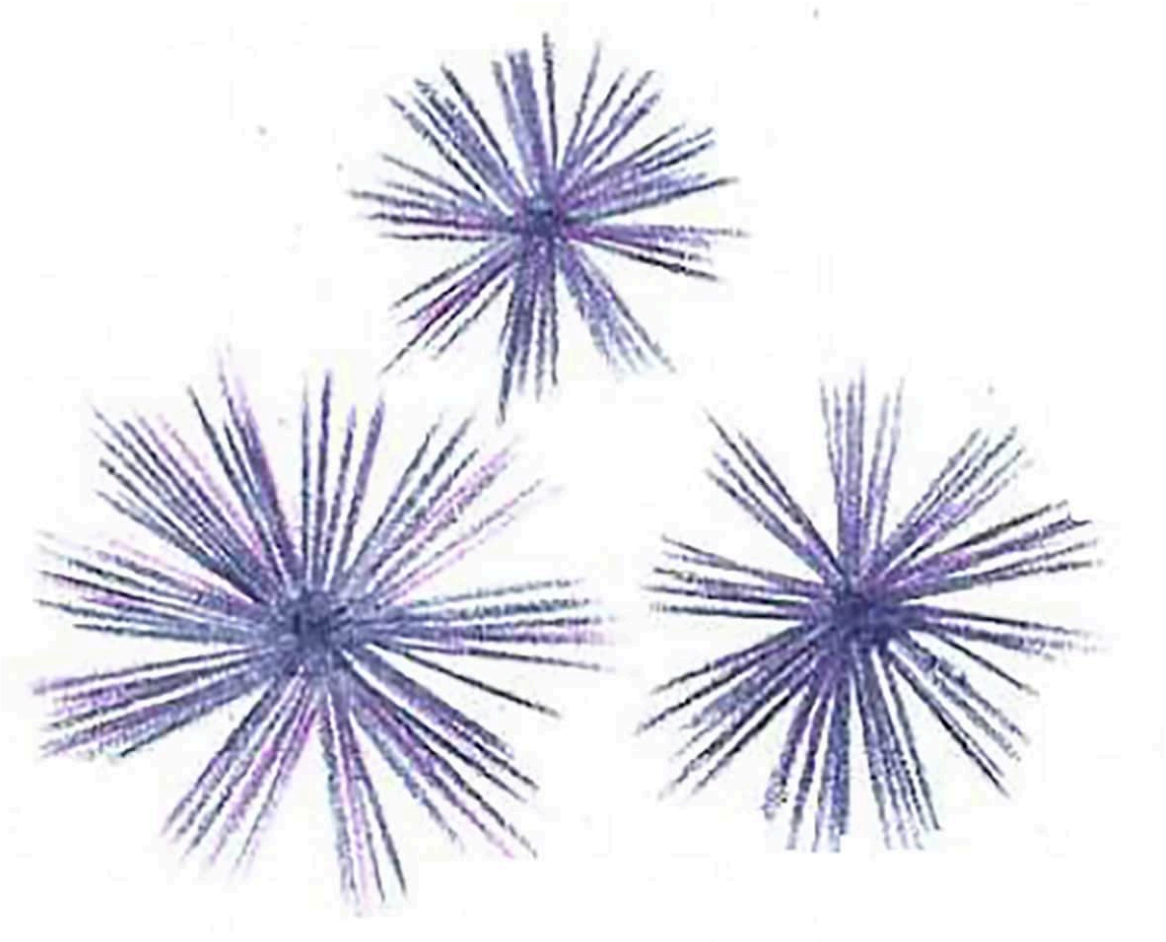
C. The incidence of basal cell carcinoma (BCC) is higher than that of squamous cell carcinoma (SCC).

D. Compared with the general population, kidney transplant recipients have a substantially higher risk for bladder cancer.

43. A 67-year-old male with a history of uric acid stone is referred by his primary care provider for acute kidney injury with serum creatinine increased to 1.8 mg/dL from 1.0 mg/dL 4 weeks prior. The patient reportedly had a urinary tract infection 2 weeks ago when he was started on ciprofloxacin. His other medications include potassium citrate 20 mmol tid and pantoprazole 20 mg daily.
Which one of the following is the MOST likely cause of his kidney injury?

Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	7.5	4.5-8.0
Specific gravity	1.021	1.005-1.025
Glucose	Negative	Negative
Ketones	Positive	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL

Color	Yellow	Yellow
Blood	Negative	Negative
Protein	Trace	Negative
Red blood cells (RBCs)	0-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	5-10	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Crystals	Needle like, stars	None



A. Acute interstitial nephritis from pantoprazole

B. Ciprofloxacin crystallization and associated nephropathy

C. Uric acid stones

D. Acute tubular injury

44. A 75-year-old male with a history of left hemiparesis and stroke is admitted from a skilled nursing facility for failure to thrive and altered mental status. Routine evaluation revealed hypernatremia of 175 mmol/L.
Physical examination: The patient is lethargic, unable to respond to questions or commands.
Vital signs: weight 60 kg, BP 92/41 mm Hg, pulse 101 beats per minute, respiratory rate 18/min, temperature 37.8 °C
Head and neck: within normal limits; dry oral mucosa
Lungs: clear to auscultation
Heart: hyperdynamic but regular heart sounds, normal S_1 and S_2
Extremities: no clubbing, cyanosis, or edema
Neurologic: arousable, moves right arm and leg only
The patient initially received 2 L of lactated Ringer bolus for rapid volume expansion. On subsequent days, the patient received between 2.0 and 2.5 L of free water daily supplement, but his serum sodium remained in the mid 150 mmol/L. The patient has also been receiving feeding of an isotonic solution via nasogastric tube. His urine output has been ranging from 1.5 to 2.0 L daily.
Laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	155	136-145 mmol/L
Potassium	4.1	3.5-5.0 mmol/L
Chloride	121	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	16	10-14 mmol/L
Blood urea nitrogen	67	8-20 mg/dL

Metabolic profile	Patient	Reference range
Creatinine	3.2	0.7-1.3 mg/dL
Glucose (fasting)	124	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	5.4	3-4.5 mg/dL
Magnesium	2.2	1.5-2.4 mg/dL
Plasma osmolarity	354	275-295 mOsm/kg H_2O
Lactate dehydrogenase	154	60-100 U/L

Urine studies: osmolality ranges between 300 and 400 mOsm/kg, sodium 50 to 60 mmol/L, potassium 16 to 23 mmol/L. A desmopressin acetate (DDAVP) challenge reveals no change in urine osmolality, urine output, or serum sodium.
What is the next BEST step?

A. Obtain copeptin level.

B. Perform a water loading test.

C. Perform a water deprivation test.

D. Reduce nasogastric feeding.

45. Which one of the following pairs BEST summarize the differences/similarities between Cerebral salt wasting (CSW) and the syndrome of inappropriate release of the antidiuretic hormone (SIADH)?

		Volume status	Uric acid	Copeptin level
A.	CSW	↓	↑	↑
	SIADH	Euvolemic	↓	↓
B.	CSW	↓	↑	↑
	SIADH	Euvolemic	↓	↑

		Volume status	Uric acid	Copeptin level
C.	CSW	↓	↓	↑
	SIADH	Euvolemic	↓	↑
D.	CSW	Euvolemic	↓	↑
	SIADH	Euvolemic	↑	↓

46. Hemodialysis should be considered for which ONE of the following cases of overdose/intoxications?
    A. Metformin-induced lactic acidosis, lactate level 10 mmol/L, arterial pH 7.2, eGFR 60 mL/min/1.73 m^2
    B. Lithium level greater than 2.0 mEq/L regardless of symptoms
    C. Salicylates with serum level 50 mg/dL and eGFR 60 mL/min/1.73 m^2
    D. Ethylene glycol with serum level greater than 50 mg/dL and visual disturbances
47. A 48-year-old female with a history of type 2 diabetes mellitus, hyperlipidemia, and chronic kidney disease stage G3aA3 is admitted for an elective laparoscopic hysterectomy for fibroids. Home medications include metformin 1,000 mg bid, lisinopril 40 mg qd, chlorthalidone 25 mg qd, and amlodipine 10 mg qd. Preoperative laboratory studies following midnight fasting:

Serum chemistry	Patient	Reference range
Sodium	137	136-145 mmol/L
Potassium	5.4	3.5-5.0 mmol/L
Chloride	103	98-106 mmol/L
Total CO_2 (bicarbonate)	23	23-28 mmol/L
Anion gap	11	10-14 mmol/L
Blood urea nitrogen	37	8-20 mg/dL

Serum chemistry	Patient	Reference range
Creatinine	1.2	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	56	mL/min/1.73 m^2
Glucose (fasting)	198	70-100 mg/dL
Albumin	3.8	3.5-5.5 g/dL

What is the MOST likely reason for her hyperkalemia?

A. Dietary nonadherence

B. Lisinopril

C. Chronic use of NSAIDs

D. Fasting blood draw

48. Hyperkalemia due to renal retention of potassium is associated with which ONE of the following conditions?

A. Gordon syndrome

B. Gitelman syndrome

C. Thrombocytosis

D. Acute myeloid leukemia

49. Which of the following statement(s) is(are) CORRECT regarding the United Network for Organ Sharing (UNOS) allocation system?

A. Zero- HLA-A, HLA-B, and HLA-DR mismatched kidneys are eligible for national sharing of donor offers.

B. Kidney transplant candidates with cPRA more than 60% are eligible for national sharing of donor offers.

C. Kidney transplant candidates with cPRA less than 50% are eligible for national sharing of donor offers.

D. Both A and B are correct.

50. Which ONE of the following causes total body potassium loss?

A. Abiraterone

B. Eplerenone

C. Barbiturate coma therapy with thiopentone

D. Finerenone

51. A 68-year-old female with a history of hypertension and atrial fibrillation presents to the emergency department for left hip pain after a fall on her left side 3 days ago. Routine laboratory evaluation revealed acute kidney injury with a rise in serum creatine from a baseline of 1.1 to 2.4 mg/dL. Her medications include metoprolol, losartan, warfarin, acetaminophen as needed for pain, and atorvastatin. The patient endorses normal oral intake and denies any recent use of NSAIDs or any newly prescribed or herbal medications.
Laboratory studies:

Serum chemistry	**Patient**	**Reference range**
Sodium	134	136-145 mmol/L
Potassium	4.1	3.5-5.0 mmol/L
Chloride	103	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Anion gap	10	10-14 mmol/L
Blood urea nitrogen	45	8-20 mg/dL
Creatinine	2.4	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	2	mL/min/1.73 m^2
Glucose (fasting)	99	70-100 mg/dL
Coagulation studies		
International normalized ratio (INR)	4.5	<1.1
Urinalysis		
Color	Pinkish red	Yellow

Serum chemistry	Patient	Reference range
Clarity/turbidity	Clear	Clear
pH	6.0	4.5-8.0
Specific gravity	1.025	1.005-1.025
Glucose	1+	Negative
Ketones	1+	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Large	Negative
Protein	>300 mg/dL	Negative
Red blood cells (RBCs)	>50	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Bacteria	None	None

Kidney ultrasound: right kidney 9 cm, left kidney 10.2 cm, normal cortical thickness, no cyst, stone, or hydronephrosis

Which one of the following is the MOST likely reason for this patient's AKI?

A. Rhabdomyolysis

B. Anticoagulant-related nephropathy (ARN)

C. Stone passage

D. Acute interstitial nephritis

52. A 77-year-old male with fecal peritonitis and acute respiratory distress syndrome (ARDS) is started on continuous kidney replacement therapy (CKRT) for oliguric AKI. He weighs 80 kg. hematocrit is 30%.
Which one of the following CKRT prescriptions is MOST appropriate?
    A. Continuous venovenous hemofiltration (CVVH) with blood flow 100 mL/min and postfilter replacement fluid (RF) 2,000 mL/h
    B. CVVH with blood flow 200 mL/min and prefilter RF 500 mL/h and postfilter RF 500 mL/h
    C. Continuous venovenous hemodialysis (CVVHD) with blood flow 150 mL/min and dialysate 1,800 mL/h
    D. CVVHDF with blood flow 250 mL/min and dialysate 1,000 mL/h and postfilter RF 200 mL/h
53. Which of the following associations is INCORRECT regarding chemotherapeutic agents?
    A. Nivolumab and pembrolizumab (anti-programmed cell death 1 [anti–PD-1] antibody checkpoint inhibitors) and acute interstitial nephritis
    B. Methotrexate and acute kidney injury due to intratubular crystallization and obstruction
    C. Lenalidomide and minimal change disease
    D. Bevacizumab (anti-vascular endothelial growth factor) and thrombotic microangiopathy
    E. Cetuximab, panitumumab (anti-epidermal growth factor receptor antibodies), and hyponatremia
54. A 35-year-old male is admitted with septic shock and acute respiratory distress syndrome from multifocal methicillin-resistant *S. aureus* pneumonia. He is started on continuous kidney replacement therapy (CKRT) for anuric acute kidney injury. Regional citrate anticoagulation is added due to frequent circuit clotting. Calcium chloride is infused in the return line of the CKRT

access. 48 hours later, you are called by the nurse for the following labs:
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	142	136-145 mmol/L
Potassium	5.1	3.5-5.0 mmol/L
Chloride	107	98-106 mmol/L
Total CO_2 (bicarbonate)	32	23-28 mmol/L
Anion gap	<6	10-14 mmol/L
Blood urea nitrogen	32	8-20 mg/dL
Creatinine	2.75	0.7-1.3 mg/dL
Total calcium	11.1	8.5-10.2 mg/dL
Ionized calcium	1.48	1.16-1.31 mmol/L

What is the next BEST step?

A. Decrease the rate of citrate.

B. Increase the rate of citrate.

C. Increase the rate of CaCl infusion.

D. Decrease the rate of CaCl infusion.

55. A 67-year-old female with a history of microscopic hematuria, proteinuria, and acute kidney injury undergoes a kidney biopsy with the following findings:
Light microscopy: lobular appearance of the tufts with mesangial and endocapillary hypercellularity, and capillary wall double contours
Immunofluorescence microscopy: positive granular staining for C3, IgG, and IgM along capillary walls and mesangium
Electron microscopy: subendothelial deposits with mesangial migration and interposition with duplication of basement

membrane forming capillary double contours. Endothelial cells with cytoplasmic tubuloreticular inclusions

Which ONE of the following diagnoses may be consistent with the kidney biopsy findings described

A. C3 glomerulonephropathy (C3G)

B. Membranoproliferative glomerular (MPGN) pattern of injury associated with a chronic active viral infection

C. IgA nephropathy (IgAN)

D. ANCA-associated glomerulonephritis

56. A high serum anion gap metabolic acidosis may be associated with intoxication of all the following alcohols EXCEPT:

A. Methanol

B. Isopropyl alcohol

C. Ethylene glycol

D. Propylene glycol

57. A 60-year-old male with a history of hypertension and heart failure with ejection fraction of 20% to 25% due to viral cardiomyopathy and anuric end stage kidney disease requiring hemodialysis support is your regular patient at the dialysis unit. He is currently being dialyzed through a central venous catheter (CVC). His K_t/V's over the past 2 months have been below goal at 1.1 despite high efficiency dialysis.

Which one of the following may be the BEST strategy to improve his K_t/V?

A. Use a dialysate with higher sodium concentrations.

B. Create an arteriovenous fistula if safely tolerated.

C. Use a dialysate with reduced osmolality.

D. Increase his dialysis treatments to 4 times weekly.

58. A 52-year-old male, peritoneal dialysis (PD) dependent for end-stage kidney failure due to membranous nephropathy, with a history of recurrent admissions for hyperkalemia presents for muscle weakness. The patient reports using a cycler at night for

four cycles of 2 L exchanges using 2.5% dextrose over 8 hours. Laboratory studies are notable for serum bicarbonate of 22 mmol/L and potassium level of 6.3 mmol/L. The patient endorses adherence to his dialysis therapy.

In addition to evaluating for the underlying cause of hyperkalemia and advising low-potassium diet, which one of the following is the next BEST step?

A. Increase current dwell volume to 2.5 L.

B. Increase peritoneal dialysis (PD) to six cycles a day.

C. Add a daytime dwell to allow for potassium removal during the daytime.

D. Change one exchange to 4.25% dextrose.

59. A 50-year-old male is evaluated for acute kidney injury after undergoing coronary artery bypass grafting with mitral valve repair. During surgery, his blood pressure (BP) fell transiently to 70/40 mm Hg, but the procedure was otherwise uneventful. His medical history includes stage 4 chronic kidney disease, type 2 diabetes, and hypertension. The patient is intubated and ventilated, receiving 50% fraction of inspired oxygen. The BP is 80/60 mm Hg while receiving an infusion of norepinephrine. Pulse oximetry is 92%. Cardiac examination is unremarkable, but lung examination reveals bibasilar crackles, and extremities have 2+ bilateral edema.

Clinical and laboratory data include the following:

	Admission	Day 3	Reference range
Weight (kg)	75	80	Variable
Urine output (mL/d)	1,820	460	Variable
Potassium (mEq/L)	4.7	5.5	3.5-5.0
Blood urea nitrogen (mg/dL)	41	98	8-20
Creatinine (mg/dL)	3	6	0.7-1.3

Continuous venovenous hemofiltration (CVVH) is begun with blood flow of 200 mL/min, ultrafiltration (UF) rate 50 mL/h, and 1 L/h prefilter and 1 L/h postfilter replacement fluid (RF). The RF contains 35 mEq/L bicarbonate and 2 mEq/L potassium.
At day 5, the patient's BP remains 80/60 mm Hg on the same rate of norepinephrine infusion, and the right leg is mottled with decreased pulses. His potassium is 5.6 mEq/L, blood urea nitrogen 28 mg/dL, and creatine kinase 25,000 IU.
Which of the following is the next BEST step in management of his renal replacement therapy?

A. Change RF to 0 L/h prefilter and 2 L/h postfilter.

B. Increase blood flow to 300 mL/min.

C. Convert to continuous venovenous hemodiafiltration with dialysate flow 2 L/h.

D. Change RF to 2 L/h prefilter and 2 L/h postfilter.

60. A 46-year-old female with a history of hypertension is referred for evaluation of hypokalemia. Her medications include potassium chloride 20 mmol/d and amlodipine 10 mg daily. Her blood pressure is 170/97 mm Hg, and pulse is 97/min.
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	140	136-145 mmol/L
Potassium	3.5	3.5-5.0 mmol/L
Chloride	100	98-106 mmol/L
Total CO_2 (bicarbonate)	29	23-28 mmol/L
Anion gap	11	10-14 mmol/L
Blood urea nitrogen	9	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	97	70-100 mg/dL

Serum chemistry	Patient	Normal range
Calcium	9.4	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL
Serologies		
Aldosterone, standing	18.8	7-20 ng/dL
Plasma renin activity	0.8	0.6-4.3 µg/L/h
Aldosterone (after IV salt loading)	18 ng/dL	<5 ng/dL

Which ONE of the following is the next BEST step?

A. Initiate adrenal vein sampling.

B. Obtain a CT of the adrenal glands.

C. Obtain cortisol level.

D. Initiate medical therapy with an a mineralocorticoid receptor antagonist.

61. A 27-year-old otherwise healthy male is admitted to the intensive care for hemorrhagic shock following a gunshot wound to his left leg. Despite hemodynamic stabilization and large-volume transfusions of blood products, the patient develops oliguric kidney failure within 4 days of hospitalization.
Urine output over the past 24 hours is 150 mL.
Physical examination
Vital signs: BP of 111/65 mm Hg, pulse 99 beats per minute, respiratory rate 16/min, temperature 37.4 °C
Neck: jugular venous pressure 10 cm, no lymphadenopathy
Oropharynx: moist oral mucosa
Lungs: bibasilar crackles
Heart: normal S_1, S_2, no murmurs, rubs, or gallops
Abdomen: nondistended, normal active bowel sounds, nontender
Extremities: trace presacral edema

Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	134	136-145 mmol/L
Potassium	4.9	3.5-5.0 mmol/L
Chloride	100	98-106 mmol/L
Total CO_2 (bicarbonate)	19	23-28 mmol/L
Anion gap	15	10-14 mmol/L
Blood urea nitrogen	69	8-20 mg/dL
Creatinine	6.7	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	11	mL/min/1.73 m^2
Glucose (fasting)	105	70-100 mg/dL

Urinalysis is bland without cells.
Which one of the following is the next BEST step?

A. Administer furosemide challenge, avoid all nephrotoxins, and adjust all medications to current kidney function.
B. Initiate continuous kidney replacement therapy.
C. Initiate intermittent hemodialysis.
D. Initiate urgent start peritoneal dialysis.

62. Which one of the following is a CORRECT statement regarding cannulation of an arteriovenous (AV) vascular access for hemodialysis?

A. Rope-ladder cannulation is not recommended due to an increased risk of infection compared with buttonhole technique.
B. Buttonhole technique requires the surgical placement of a "button" port of entry into the AV access.

C. Buttonhole technique is associated with lower infection risk compared with rope-ladder technique.

D. Buttonhole technique may be associated with lower pain scores with prolonged use compared with rope-ladder technique.

63. A 32-year-old male with no past medical history presents to the emergency department with a 7 to 10-day history of constant headaches and fatigue followed by gingival bleeding and palpitations 2 to 3 days prior to presentation. Review of systems is positive for a history of dark brown urine over the past few days. The patient denies any recent history of infections, fevers, chills, or diarrhea.

Physical examination is notable for a pale-appearing male, oral mucosa with several foci of gingival hemorrhages. Neurologic examination is notable for slow mentation and difficulty with word finding, otherwise nonfocal.

Family history is negative for any similar problem.

Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	4.1	4-10 × 10^3/mL
Hemoglobin	6.7	Male: 14-17 g/dL
Hematocrit	20.7	Male: 45%-52%
Platelet count	15	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Serum chemistry	**Patient**	**Reference range**
Sodium	136	136-145 mmol/L
Potassium	5.6	3.5-5.0 mmol/L
Chloride	102	98-106 mmol/L
Total CO_2 (bicarbonate)	20	23-28 mmol/L

Hematology	Patient	Reference range
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	25	8-20 mg/dL
Creatinine	1.5	0.7-1.3 mg/dL
Glucose (fasting)	80	70-100 mg/dL
Lactate dehydrogenase	1,767	9-10.5 mg/dL
Haptoglobin	40	3-4.5 mg/dL
Indirect bilirubin	3.0	3.5-5.5 g/dL
Coagulation studies		**Reference range**
Activated partial thromboplastin time	31.2	25-35 s
Prothrombin time	14.5	11-13 s
INR	1.2	

Reticulocyte count 17.8%
Peripheral blood smear is positive for schistocytes.
Direct antiglobulin test is negative.
Brain CT is negative for bleed.
PLASMIC score: 6
Which one of the following is the next BEST step?

A. Provide broad antibiotic coverage.

B. Supportive care and transfuse blood products as needed.

C. Perform plasma exchange (PLEX).

D. Perform emergent endoscopy.

64. A 53-year-old male with a history of bipolar disorder and lithium-induced nephrogenic diabetes insipidus (DI) is referred to you for the treatment of nephrogenic DI. His referral psychiatrist is unable to discontinue the patient's lithium due to concerns for severe depressive phase and associated suicidal ideation.

What is the BEST therapeutic option?

A. Thiazide

B. Amiloride

C. Desmopressin acetate (DDAVP)

D. Tolvaptan

65. A patient undergoing hemodialysis receives a drug prior to dialysis. His predialysis plasma concentration of the drug is 60 mg/dL, and postdialysis plasma concentration is 30 mg/dL. The dialysis session was performed over 4 hours at a blood flow rate (BFR) of 400 mL/min. What is the clearance of the drug?

A. 200 mL/min

B. 160 mL/min

C. 80 mL/min

D. 60 mL/min

66. Which one of the following statements is CORRECT regarding the acute management of thrombotic thrombocytopenic purpura (TTP) due to the presence of ADAMTS13 inhibitory autoantibodies?

A. Immediate plasmapheresis with 5% albumin replacement should be performed.

B. Immediate caplacizumab therapy to reduce ADAMTS13 autoantibody production is indicated.

C. Immediate therapy with rituximab (RTX) is indicated.

D. Immediate plasma exchange should be performed.

67. A 32-year-old female with a history of bipolar disorder is admitted for altered mental status.
Routine evaluation revealed an serum creatinine of 2.1 mg/dL (up from a baseline of 1.0 mg/dL 1 month prior) and a lithium level of 3.0 mEq/L.
What is the next BEST step?

A. Initiate prolonged kidney replacement therapy (KRT) now.

B. Provide supportive airway and protect airway.

C. Initiate alkalinization and IV fluid support.

D. Initiate KRT when lithium level exceeds 3.5 mEq/L.

68. A 22-year-old 60-kg female with a history of minimal change disease (MCD) presents to you for a second opinion. She was started on prednisone by her nephrologist 3 months ago. She endorses compliance to prednisone 60 mg daily, furosemide 40 mg daily, and potassium chloride 20 mEq daily. Physical examination is notable for pedal edema 2+ up to knees bilaterally. She has not noticed any difference in her edema since starting prednisone.

Laboratory studies:

	Today	3 mo ago	Reference range
Sodium	133	132	136-145
Potassium	3.5	4.0	3.5-5.0
Chloride	105	105	98-106
Total CO_2	25	23	23-28
Blood urea nitrogen	17	11	8-20
Creatinine	0.8	1.0	0.5-1.1
Glucose	121	95	70-99, fasting
Albumin	1.6	1.5	3.5-4.8

Urinalysis reveals specific gravity 1.017, pH 6.0, greater than 600 mg/dL protein, no glucose, 0 to 3 WBCs/HPF, and 5 to 10 RBCs/HPF. There are 0 to 5 hyaline casts. Urine protein to creatinine ratio is 6.7 g/g, urine albumin to creatinine ration is 6.1 g/g. Her uPCR 4 weeks ago was 6.2 g/g.

A kidney biopsy performed 3 months ago yielded eight glomeruli: five on light microscopy revealed MCD, two on immunofluorescence microscopy lacked staining for Igs or

complements, and one on electron microscopy revealed foot podocyte effacement more than 80%.
Which one of the following is the next BEST step?

A. Increase prednisone to 80 mg daily.

B. Repeat kidney biopsy.

C. Add a calcineurin inhibitor.

D. Initiate rituximab.

69. Which one of following has not been reported to cause both Fanconi syndrome AND nephrogenic diabetes insipidus?

A. Tenofovir

B. Abacavir

C. Lamivudine

D. Cisplatin

70. A 44-year-old normotensive male presents with the following urine studies:
Urine sodium 17 mmol/L, potassium 15 mmol/L, chloride 11 mmol/L, urine pH 6.0
Which ONE of the following diagnoses is consistent with having urine studies above?

A. Gitelman syndrome

B. Bartter syndrome

C. Ketoacidosis

D. Acute vomiting

71. An 82-year-old female with a history of rheumatoid arthritis is admitted for altered mental status. Evaluation revealed salicylate level 100 mg/dL, severe metabolic acidosis with blood pH of 7.1, and oliguric acute kidney injury with serum creatinine of 5.7 mg/dL from a baseline of 0.9 mg/dL 1 month prior.
In addition to protecting the airway, which one of the following is the BEST management option?

A. Fluid resuscitate with 5% dextrose (D5) normal saline

B. Fluid resuscitate with lactated Ringer solution

C. Fluid resuscitate with D5 sodium bicarbonate solution

D. Initiate hemodialysis along with fluid resuscitation with D5 bicarbonate solution.

72. A 27-year-old male with no known medical history presents with sudden-onset severe proximal weakness followed by generalized muscle paralysis 5 hours after a 5-mile race with his college friends. He denies any history of trauma or similar episode in the past or use of herbal, recreational, or over-the-counter drugs. Physical examination is notable for decreased muscle strength and tone in all extremities (4/5 strength), more prominent in proximal muscles (3+/5), and hypoactive deep tendon reflexes. Laboratory evaluation reveals serum potassium of 2.2 mmol/L, magnesium 1.8 mg/dL, sodium 134 mmol/L, and total CO_2 22 mmol/L (serum bicarbonate). Urine studies reveal sodium 50 mmol/L, chloride 80, and urine potassium-to-creatinine concentration ratio 2.5 mmol/g creatinine. Thyroid function is within normal limits. An electrocardiogram reveals prolonged PR interval, T-wave inversion, QT prolongation, and U waves. Potassium supplement promptly corrects his symptoms and ECG changes.
What is the MOST likely diagnosis?

A. Severe hypovolemia-induced hypokalemia

B. Ongoing loop diuretic abuse

C. Hypokalemic period paralysis

D. Alcohol abuse

73. All of the following contribute to post-transplantation hypophosphatemia EXCEPT:

A. Fibroblast growth factor 23

B. Metabolic alkalosis

C. Glucosuria

D. Corticosteroid

74. A 55-year-old 60-kg female with a history of alcohol abuse is admitted to the ICU for severe pneumonia. Upon admission, the

patient rapidly deteriorates and is intubated.
Urine output over the past 12 hours: 250 mL
Physical examination
Vital signs:
Baseline BP 95/40 mm Hg, pulse 95 beats per minute
Passive leg raising BP 105/47 mm Hg, pulse 94 beats per minute
Neck: no jugular vein distention, no lymphadenopathy
Lungs: no rales appreciated
Heart: normal S_1, S_2, no murmurs, rubs, or gallops
Abdomen: obese, hypoactive bowel sounds, no hepatomegaly
Extremities: no edema
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	130	136-145 mmol/L
Potassium	4.9	3.5-5.0 mmol/L
Chloride	95	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	88	8-20 mg/dL
Creatinine	5.6	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	8	mL/min/1.73 m^2
Glucose (fasting)	99	70-100 mg/dL
Coagulation studies		
INR	1.2	<1.1
Urinalysis		
Color	Pinkish red	Yellow

Serum chemistry	Patient	Reference range
Clarity/turbidity	Clear	Clear
pH	6.0	4.5-8.0
Specific gravity	1.025	1.005-1.025
Glucose	Negative	Negative
Ketones	1+	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Positive	Negative
Urobilirubin	1.3	0.5-1.0 mg/dL
Blood	Small	Negative
Protein	100 mg/dL	Negative
Red blood cells (RBCs)	0-5	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	30	<15-20 squamous epithelial cells/HPF
Bacteria	Few	None

Which one of the following is the BEST management strategy?

A. Initiate intermittent hemodialysis.

B. Initiate continuous kidney replacement therapy.

C. Provide fluid challenge.

D. Continue to monitor and initiate HD when there is evidence of volume overload and/or life-threatening electrolyte disturbances.

75. A 33-year-old female with a history of hypertension (HTN) and uterine fibroid is referred to your clinic for evaluation and

management of secondary HTN. Her current medication is amlodipine. Her BP is 179/102 mm Hg and pulse is 85/min. Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	135	136-145 mmol/L
Potassium	3.3	3.5-5.0 mmol/L
Chloride	95	98-106 mmol/L
Total CO_2 (bicarbonate)	30	23-28 mmol/L
Blood urea nitrogen	9	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	97	70-100 mg/dL
Calcium	9.4	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL
Magnesium	1.9	1.5-2.4 mg/dL
Serologies		
Renin activity	8.2	0.6-4.3 µg/L/h
Aldosterone	21	7-20 ng/dL
Normetanephrine	148	18-111 pg/mL
Metanephrine	80	12-60 pg/mL
24-h urine free cortisol excretion	8	3.5-45 µg

Venous blood gas: pH 7.42, pCO_2 45 mm Hg, HCO_3^- 29 mmol/L

Which one of the following may be a possible diagnosis for the patient's HTN?

A. Licorice ingestion

B. Dexamethasone-suppressible hyperaldosteronism

C. Unilateral renal artery stenosis

D. Gain-of-function mutation of the mineralocorticoid receptor

76. A 72-year-old male develops acute kidney injury post coronary artery bypass surgery and aortic valve repair. He weighs 90 kg. His hematocrit is 30%. A double-lumen short-term dialysis catheter is placed in his right internal jugular vein with the tip at the cavoatrial junction.
Continuous venovenous hemodiafiltration (CVVHDF) is initiated using the following prescription:
Blood flow rate 120 mL/min
Dialysate rate 1,500 mL/h
Postfilter replacement fluid (RF) rate 800 mL/h
Fluid removal 200 mL/h
The circuit is anticoagulated with citrate infused via a port near the arterial access. His postfilter ionized calcium levels are less than 0.35 mmol/L.
The patient develops acute mental status changes, and CVVHDF is disconnected for head CT. When the patient returns from CT, he is restarted on continuous kidney replacement therapy by the ICU nurse on the same prescription, except with a blood flow of 200 mL/min. Four hours later, the circuit clots.
What is the MOST likely cause of the premature clotting of the circuit?

A. Too short dialysis catheter length

B. Increased filtration fraction (FF)

C. Subtherapeutic citrate dose

D. Inadequate dialysis dose

77. Which one of the following medications may MOST likely induce clinical manifestations similar to those seen in preeclampsia (eg, HTN, proteinuria, thrombotic microangiopathy)?

A. Venlafaxine

B. Cyclooxygenase-2 (COX-2) inhibitors

C. Inhibitors of vascular endothelial growth factor (VEGF)

D. Endothelin receptor antagonists

78. Which one of the following statements regarding water treatment for HD is CORRECT?
    A. The required steps in water treatment include carbon filtration and reverse osmosis.
    B. The required steps in water treatment include carbon filtration, softeners, reverse osmosis, deionization, and ultrafilter/endotoxin filter.
    C. Reverse osmosis removes chlorine and chloramine and organic contaminants.
    D. Carbon filtration removes residual ions by exchange of resins made up of both cations and anions (eg, hydrogen and hydroxyl ions, respectively) to exchange for negatively and positively charged ionic contaminants, respectively, following reverse osmosis.
79. A 44-year-old male presents for a routine physical examination for his new job as a commercial pilot. His primary care provider consults you for abnormal laboratory studies. The patient has no known medical history but recalls he was told the previous year that he had high BP and potassium level when he presented to urgent care for a leg laceration. He was advised to follow up but never had the chance to make an appointment to see his provider. Review of systems is negative.
    Medications: none
    Physical examination is unremarkable, except for elevated BP 158/92 mm Hg, pulse 78/min.
    Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	135	136-145 mmol/L
Potassium	5.7	3.5-5.0 mmol/L
Chloride	99	98-106 mmol/L

Serum chemistry	Patient	Normal range
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Blood urea nitrogen	14	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	99	70-100 mg/dL
Calcium	9.7	9-10.5 mg/dL
Phosphorus	4.2	3-4.5 mg/dL
Magnesium	2.1	1.5-2.4 mg/dL

After confirming that the patient does indeed have hypertension and similar laboratory studies in the past, which one of the following may be the BEST antihypertensive agent?

A. Loop diuretic

B. Amlodipine

C. Thiazide

D. Hydralazine

80. A 33-year-old female with no past medical history is referred to the renal clinic for a gradual increase in serum creatinine from 0.8 to 1.6 mg/dL over the past year. Review of systems is notable for a history of dry eyes and mouth noted over the past year. Initial evaluation reveals several foci of small calcifications in both kidneys.
Physical examination: well appearing, no acute distress
Vital signs: weight 55 kg, BP 115/61 mm Hg, pulse 76 beats per minute, respiratory rate 14/min, temperature 37.2 °C
Oropharynx: dry oral mucosa
Lungs: clear to auscultation
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: normal bowel sounds, soft, nondistended, nontender, no hepatomegaly

Extremities: no edema
Neurologic examination: nonfocal
Kidney ultrasound reveals normal-sized kidneys without evidence of hydronephrosis, cysts, stones, or mass. Urinalysis is bland with 1+ proteinuria with 0 to 3 red blood cells per high powerfield, 0 to 3 white blood cells per high powerfield, and no cast. Urine protein to creatinine ratio is 1.2 g/g, and urine albumin to creatinine ratio is 0.25 g/g.
Further serologies confirm the diagnosis of Sjögren syndrome.
Which one of the following is the MOST likely lesion on kidney biopsy?

A. Focal and segmental glomerulosclerosis

B. IgA nephropathy

C. Chronic interstitial nephritis

D. Xanthogranulomatous pyelonephritis

81. Which one of the following is NOT an adverse effect associated with tolvaptan?

A. Nephrogenic diabetes insipidus (DI)

B. Transaminitis

C. Hematuria

D. Hyperuricemia

82. A 32-year-old female with no past medical history is brought by her family for progressive memory loss. The patient endorses starting a calorie-restricted diet and drinking 5 L of water daily to cleanse her body for the past 2 months. Routine chemistry reveals a serum sodium of 120 mmol/L. Urine studies reveal an osmolality of 98 mOsm/kg, sodium less than 10 mmol/L, and potassium 15 mmol/L.
The patient is admitted for close monitoring of her serum sodium concentration.
What is the BEST treatment option?

A. Fluid restriction to 1 L a day.

B. Infuse 300 mL of 3% and restrict daily fluid intake to 1.5 L a day.

C. Provide desmopressin acetate (DDAVP).

D. Reduce fluid intake to match 50% to 70% of urine output while increasing solute intake.

83. Which ONE of the following serum laboratory sets belongs to a patient who has moderate-to-severe isopropyl alcohol (rubbing alcohol) intoxication?

Serum	Bicarbonate	Anion gap	Ketones	Osmolality gap
A	↓	↑	↑	↑
B	Normal	Normal	↑	↑
C	↓	↑	Normal	Normal
D	Normal	Normal	↑	Normal

84. Which one of the following conditions has the CORRECT neurohormonal profile?

		Renin activity	Plasma aldosterone	Urine cortisol	Urine cortisone
A.	Dexamethasone-suppressible hyperaldosteronism	↓	↓ or normal	↑	↓
B.	Liddle syndrome	↓ or normal	↑	↓	↓
C.	Unilateral renal artery stenosis	Normal	↑	↓	↓
D.	Apparent mineralocorticoid excess (AME) syndrome	↓ or normal	↓ or normal	↑	↓

85. A 56-year-old male with ischemic cardiomyopathy and ejection fraction of 25% to 30% is admitted for short of breath and acute

decompensated heart failure Chart review suggests that he is overloaded by 10 to 15 L. The patient is given bumetanide 2 mg intravenously every 6 hours and metolazone 5 mg bid with relatively good response. His net daily fluid balance ranges between negative 1.5 and 2.0 L over the last 4 days. The patient endorses feeling much better since admission.
Most recent laboratory studies:

Metabolic profile	Patient	Reference range
Sodium	132	136-145 mmol/L
Potassium	3.1	3.5-5.0 mmol/L
Chloride	121	98-106 mmol/L
Total CO_2 (bicarbonate)	29	23-28 mmol/L
Anion gap	16	10-14 mmol/L
Blood urea nitrogen	47	8-20 mg/dL
Creatinine	1.2	0.7-1.3 mg/dL
Glucose (fasting)	112	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	5.4	3-4.5 mg/dL
Magnesium	2.1	1.5-2.4 mg/dL

Blood gas pH 7.44, pCO_2 44 mm Hg, pO_2 80 mm Hg, oxygen saturation 92%
Which one of the following is the next BEST step?

A. Add acetazolamide.

B. Add spironolactone.

C. Start dialysis for ultrafiltration.

D. Convert to bumetanide drip.

86. A dialysis unit calls 911 for multiple patients coding from acute onset chest and back pain, dyspnea, and severe bradycardia during the very first shift of hemodialysis treatments. The bloodlines in these patients were noted to be deep red in color. The unit medical director orders to immediately stop all dialysis treatments and discard all blood in the circuits.
Which one of the following is the MOST likely problem?

A. There has been an intentional poisoning of drinking water with high-dose β-blocker by a disgruntled dialysis nurse.

B. The ultrafilter/endotoxin filter has not been changed overnight.

C. Softeners were not used in the water treatment process.

D. There has been damage to the carbon filtration system.

87. A 63-year-old male with a history of diabetes mellitus and hypertension presents for newly diagnosed distal renal tubular acidosis type 4 secondary to hypoaldosteronism.
Medications: insulin, atorvastatin, amlodipine, chlorthalidone, and aspirin. The patient was previously told that he cannot tolerate renin-angiotensin inhibitors due to hyperkalemia.
Physical examination
Vital signs: weight 72 kg, body mass index 29 kg/m^2, BP 128/94 mm Hg, pulse 76 beats per minute, respiratory rate 15/min, temperature 37.2 °C
Neck: no jugular vein distention
Lungs: clear to auscultation bilaterally
Heart: no murmurs, gallops, or rubs
Abdomen: obese, normal bowel sounds, nontender, no hepatosplenomegaly
Extremities: 1+ up 2/3 bilateral legs
Neurologic examination: nonfocal
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	134	136-145 mmol/L
Potassium	5.6	3.5-5.0 mmol/L

Serum chemistry	Patient	Reference range
Chloride	108	98-106 mmol/L
Total CO_2 (bicarbonate)	14	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	17	8-20 mg/dL
Creatinine	1.1	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	75	mL/min/1.73 m^2
Glucose (fasting)	125	70-100 mg/dL

Which one of the following is the next BEST step?

A. Start zirconium cyclosilicate (Lokelma) daily.

B. Start fludrocortisone and furosemide.

C. Start fludrocortisone and advise low-sodium diet.

D. Maximize thiazide dose.

88. A 96-year-old female is referred for evaluation of a renal cyst seen on CT described as a single cyst measuring 4.0 × 4.7 × 2.1 cm^3 with two hairline thin septations with fine calcifications in one septum.
Which one of the following is the BEST next step?

A. Follow-up at 6 and 12 months, then annually for 5 years to assess for changes.

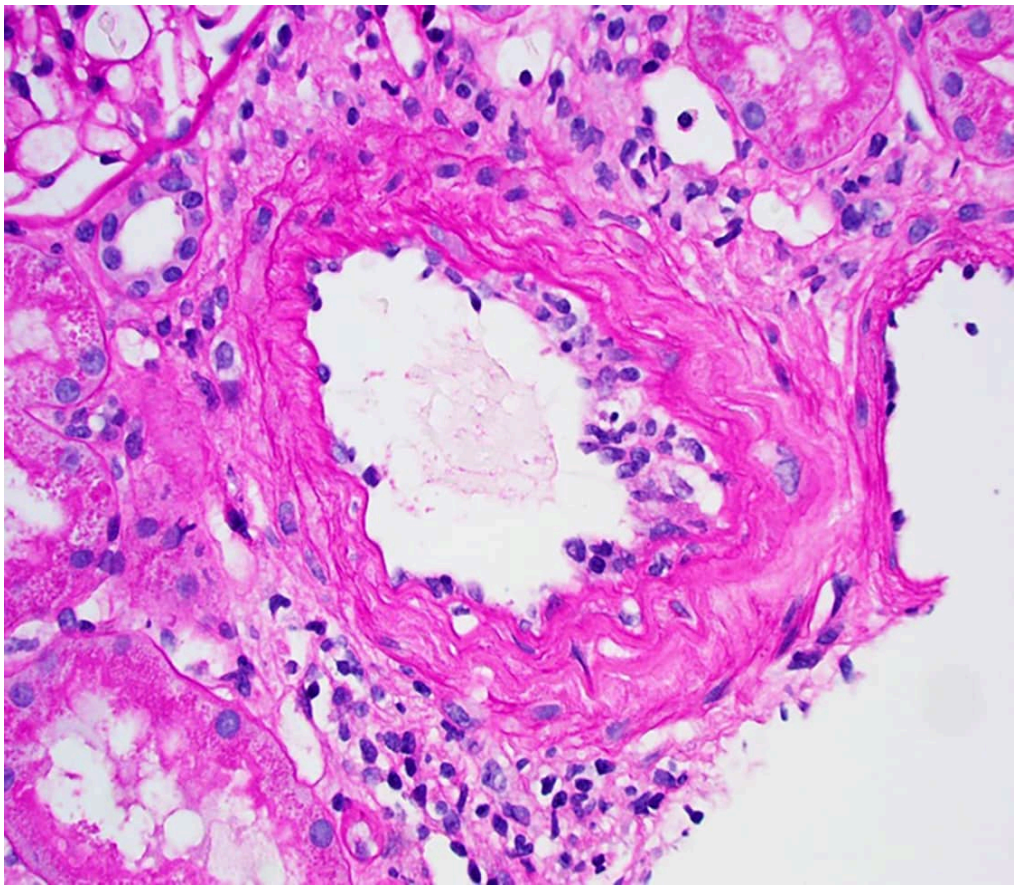
B. Benign simple cyst, no follow-up is required.

C. Follow-up at 3 and 6 months, then annually for 5 years to assess for changes.

D. Obtain CT with contrast.

89. A 39-year-old man with ESKD secondary to IgAN received a deceased donor kidney 3 years ago. He was induced with basiliximab and methylprednisolone and was maintained on standard triple immunosuppressive regimen consisting of

tacrolimus, mycophenolate mofetil, and prednisone. He did well until 3 months ago when he was hospitalized for pseudomonas and *E. coli* bacteremia. Mycophenolate mofetil was held in the setting of infection. He was initially treated with IV cefpodoxime, which was transitioned to oral ciprofloxacin on hospital day 7. Repeat blood culture on hospital day 5 was negative. He was subsequently discharged home on hospital day 8. Two weeks after his hospital discharge, he was seen in the clinic and was noted to have acute kidney injury. Allograft ultrasound Doppler was unremarkable. Allograft biopsy is shown below.



Periodic acid-Schiff stain, 400×

Laboratory studies on the day of biopsy:
Creatinine 2.8 mg/dL (baseline 1.0-1.2 mg/dL)
Hemoglobin 10.2 g/dL
Hematocrit 30.6%

Urinalysis Unremarkable
Blood tacrolimus trough level 7.8 ng/mL (target 6-9 ng/mL)
C4d staining Negative
Donor specific antibody (DSA) Pending
Which ONE of the following is the MOST appropriate treatment for this patient?

A. High-dose IV methylprednisolone

B. Antithymocyte globulin (ATG)

C. Intravenous immunoglobulin (IVIG)

D. Eculizumab

90. A 72-year-old male, weighing 60 kg, with a history of severely enlarged prostate presents with urinary obstruction and acute kidney failure with an serum creatinine (SCr) of 6.5 mg/dL. A Foley is placed for drainage. The patient's SCr improved over the next 5 days to 1.5 mg/dL. Over the next 3 days, however, it is noted that the patient's urine output gradually increases up to 4 L/d. In anticipation of postobstructive diuresis, the patient is given half-normal saline infusion to match half of the patient's urine output rate. He has been eating approximately 80% of his meals daily since admission.
His current laboratory studies are as follows:

Metabolic profile	Patient	Reference range
Sodium	134	136-145 mmol/L
Potassium	4.1	3.5-5.0 mmol/L
Chloride	102	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	27	8-20 mg/dL
Creatinine	1.2	0.7-1.3 mg/dL

Metabolic profile	Patient	Reference range
Glucose (fasting)	105	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	5.4	3-4.5 mg/dL
Magnesium	2.1	1.5-2.4 mg/dL
Plasma osmolarity	295	275-295 mOsm/L

24-hour urine studies: volume 4.2 L, creatinine 1,117 mg, osmolality 252 mOsm/kg, sodium 75 mmol/L, potassium 27 mmol/L

Which one of the following statements is MOST accurate?

A. The patient has an osmotic diuresis from the accumulated BUN following the relief of his obstruction.

B. The patient has an osmotic diuresis from the ongoing saline infusion and mild aquaresis.

C. The patient only has an aquaresis, which is likely from nephrogenic diabetes insipidus associated with obstructive uropathy.

D. The patient is having polyuria because of his ongoing half-normal saline infusion.

91. All of the following drugs can cause acute interstitial nephritis (AIN) and/or chronic interstitial nephritis AND hypomagnesemia EXCEPT:

A. Pantoprazole

B. Synthetic cannabinoids

C. Cisplatin

D. Thiazide diuretics

92. Which ONE of the following is consistent with hypovolemia-induced hyperaldosteronism?

	Renin	Aldosterone	Urine potassium	Serum potassium
A.	↑	↑	↑	↓
B.	↑	↑	↓ or normal	Normal
C.	Normal	↑	↑	↓
D.	↓	↑	Normal	Normal

93. A 45-year-old female presents to the emergency department for dizziness. She is visiting her sister for the weekend and does not have her medical records but knows that she has adenocarcinoma of the lung. She mentioned that her most recent chemotherapy with cisplatin was complicated by severe electrolyte disturbances. Which one of the following is MOST consistent with cisplatin-induced electrolyte disturbances and reason for the patient's dizziness?

	Serum chemistry				Urine studies		
	Sodium (mmol/L)	Potassium (mmol/L)	Bicarbon-ate (mmol/L)	Glucose (mg/dL)	Sodium (mmol/L)	Glucose (0-4+)	Protein (0-4+)
A.	121	3.8	20	254	25	1+	1+
B.	118	5.6	32	105	154	negative	Negative
C.	154	5.7	32	292	<10	2+	Negative
D.	125	3.5	22	118	135	1+	1+

94. A 36-year-old female received a deceased donor kidney transplant in June 2020. Her maintenance immunosuppressive regimen consisted of tacrolimus 2 mg bid, mycophenolate mofetil 1,000 mg bid, and prednisone 5 mg daily. Her other medications include diltiazem CR 180 mg daily, atorvastatin 20 mg daily, pantoprazole 40 mg daily, and losartan 25 mg daily. She had excellent graft function and did well until 1 month ago when she was diagnosed with pulmonary tuberculosis for which she was started on isoniazid, rifampin, pyrazinamide, and ethambutol. She reports initial improvement in her appetite and energy level until 1 week ago when she presented to the emergency department with

nausea, vomiting, fatigue, and mild decreased urine output. She reports vomiting all her pills the day prior to admission. On examination, she is afebrile, BP 130/80 mm Hg, and pulse of 80 beats/min. Her lungs are clear to auscultation bilaterally, and her allograft is nontender. She has trace peripheral edema.
Laboratory studies:

Serum chemistry	Patient	Reference range
Sodium	133	136-145 mmol/L
Potassium	3.8	3.5-5.0 mmol/L
Chloride	99	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	13	10-14 mmol/L
Blood urea nitrogen	80	8-20 mg/dL
Creatinine	5.8	0.7-1.3 mg/dL
Glucose (fasting)	118	70-100 mg/dL
Tacrolimus trough	<0.5	6-10 ng/mL

Allograft biopsy shows acute T-cell mediated rejection type 2A and antibody-mediated rejection.
Which one of the following MOST likely accounts for this patient's subtherapeutic tacrolimus level?

A. Ethambutol

B. Rifampin

C. Missing a dose of diltiazem

D. Isoniazid

95. A 67-year-old hemodialysis-dependent female due to end stage kidney disease from diabetes mellitus, atrial fibrillation, and HTN is hospitalized for left lower leg cellulitis. Her net fluid balance ranges from 1 to 2 L positive daily.

Medications: metoprolol 50 mg bid, insulin, losartan, spironolactone, furosemide, apixaban, sevelamer carbonate, cholecalciferol

Physical examination is notable for BP of 130/80 mm Hg, irregular heart rate at approximately 60 to 70 beats per minute, clear lungs, and absence of pedal edema.

Dialysis prescription: ultrafilter 2 to 3 L as tolerated; dialysate: sodium 140 mmol/L, potassium 3 mmol/L, bicarbonate 30 mmol/L, calcium 2.25 mEq/L; BFR 300 mL/min; dialysate flow rate 500 mL/min. Dialysate temperature is set at 1 °C below body temperature.

Review of her dialysis record indicates that the patient tends to get more hypertensive and tachycardic toward the end of her dialysis treatment.

Which one of the following may BEST control her hemodynamic parameters toward the end of her dialysis treatment?

A. Increase metoprolol dose to the maximum tolerable dose.

B. Switch metoprolol to carvedilol.

C. Add diltiazem or verapamil and evaluate for underlying ischemic heart disease.

D. Increase dialysate temperature to body temperature.

96. A 42-year-old male with acute respiratory failure due to severe pneumonia requires maximum mechanical ventilation with fraction of inspired oxygen of 100% to maintain blood oxygen saturation of 85% to 90%. His predialysis venous blood gas reveals a pH of 7.42, pCO_2 24 mm Hg, and bicarbonate 15 mEq/L. The patient also requires hemodialysis support daily for kidney failure and high catabolic state. Serum potassium ranges between 4.5 and 4.8 mEq/L.

Which one of the following is the MAXIMUM bicarbonate concentration for his dialysate?

A. 35 to 40 mEq/L

B. 30 to 35 mEq/L

C. 30 to 40 mEq/L

D. 20 to 25 mEq/L

97. A 44-year-old female with a history of diabetes mellitus, chronic kidney disease stage G5A3 due to lupus nephropathy, hypertension, anemia, obesity class 2, and atrial fibrillation presents with a poor healing painful ulcerated 3 × 4 cm lesion with black eschar and surrounding leather-like skin on her right thigh. Skin biopsy revealed calcification and fibrointimal hyperplasia of subcutaneous and dermal arteries and arterioles and septal panniculitis. Iron studies suggest iron stores have been repleted.

Medications: prednisone, sevelamer carbonate, warfarin, iron sulfate, calcitriol

In addition to providing wound care and holding iron and calcitriol, which one of the following is the next BEST step?

A. Taper prednisone off if possible and consider switching warfarin to a direct oral anticoagulant.

B. Taper prednisone off and discontinue sevelamer carbonate.

C. Switch warfarin to direct oral anticoagulant.

D. Discontinue warfarin and taper prednisone off.

98. A 42-year-old female with a history of diffuse scleroderma presents with acute kidney injury with serum creatinine of 2.4 mg/dL (1.1 mg/dL 2 weeks prior). Urinalysis is notable for new-onset proteinuria 200 mg/dL and hematuria 10 to 15 red blood cells per high powerfield. Complete blood count is notable for hemolytic anemia and platelets 50/µL. Physical examination reveals BP of 140/82 mm Hg and pulse 99 beats per minute. Her baseline systolic blood pressure is in the range of 100 to 110 mm Hg.

Which one of the following is a CORRECT statement?

A. The patient presents with scleroderma renal crisis (SRC).

B. The patient has AKI unrelated to scleroderma.

C. Blood pressure is best managed with a calcium channel blocker (CCB) in this case.

D. Blood pressure is best managed with a β-blocker in this case.

99. A 65-year-old female with a history of systemic scleroderma, myositis (recently treated with high-dose prednisone), pulmonary hypertension, and slowly increasing serum creatinine over the past 2 month, now presents with blood pressure of 178/102 mm Hg, oliguric acute kidney injury, thrombocytopenia, undetectable haptoglobin, increased lactate dehydrogenase level, volume overload, and congestive heart failure. ADAMTS13 is negative.
In addition to providing diuretic therapy, which one of the following is the BEST therapeutic option?

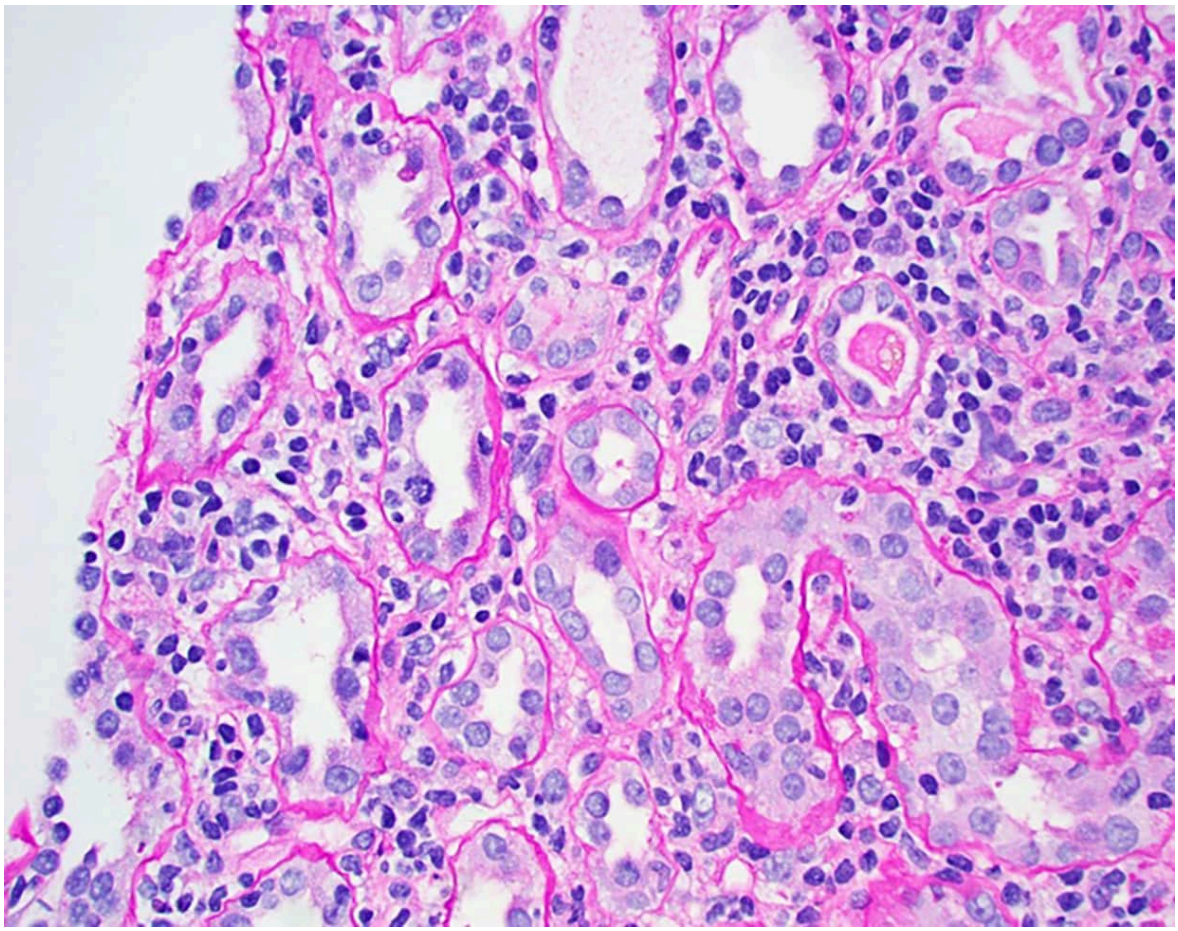
A. Eculizumab

B. Angiotensin converting enzymbe inhibitor (eg, captopril)

C. β-Blocker (eg, labetalol)

D. Endothelin receptor antagonist (eg, bosentan)

00. A 21-year-old male with ESKD secondary to alport syndrome (AS) received a living unrelated kidney transplant from a family friend 8 months ago. He was seen in a clinic for his routine monthly follow-up. On laboratory examination, he was noted to have AKI with creatinine of 1.8 mg/dL (baseline 0.9-1.1 mg/dL). Tacrolimus level was 9.1 mg/dL (target 8-10 mg/dL). Urinalysis showed trace protein, 0 to 3 WBCs/HPF, 5 to 10 RBCs/HPF, and trace leukocyte esterase.
Allograft biopsy is shown below.



Which one of the following is the MOST appropriate treatment for this patient?

A. Defer treatment pending electron microscopy to rule out recurrent alport syndrome (AS)

B. IV antibiotics

C. Rituxan

D. High-dose IV methylprednisolone

01. A 47-year-old male with alcohol-induced cirrhosis presents with 1-week history of nausea, vomiting, and poor oral intake.
Medications: furosemide 40 mg bid, spironolactone 50 mg bid, omeprazole 20 mg daily, folate 1 mg daily, multivitamin 1 mg daily, lactulose 30 mL daily
Physical examination: chronically ill appearing
Vital signs: weight 80 kg, BP 92/41 mm Hg, pulse 101 beats per minute, respiratory rate 20/min, temperature 37.2 °C

Head and neck: within normal limits; dry oral mucosa
Lungs: clear to auscultation
Heart: hyperdynamic regular heart sounds, normal S_1 and S_2
Abdomen: distended, normal active bowel sounds
Extremities: no clubbing, cyanosis, or edema
Skin: wrinkled in all extremities
Neurologic: nonfocal

Metabolic profile	Patient	Reference range
Sodium	127	136-145 mmol/L
Potassium	3.4	3.5-5.0 mmol/L
Chloride	102	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	7	10-14 mmol/L
Blood urea nitrogen	27	8-20 mg/dL
Creatinine	2.4 (1.1, 2 weeks ago)	0.7-1.3 mg/dL
Glucose (fasting)	73	70-100 mg/dL
Calcium	8.2	9-10.5 mg/dL
Phosphorus	5.4	3-4.5 mg/dL
Magnesium	1.6	1.5-2.4 mg/dL
Albumin	2.8	3.5-5.5 g/dL

Hemoglobin is 10.1 g/dL.
Which one of the following is the BEST volume expander for the patient at this time?

A. 25% albumin

B. Normal saline

C. Packed red blood cells

D. Lactated Ringer

02. Which of the following drug(s) is/are safe to be used in pregnancy?

A. Mycophenolate acid derivatives

B. Mammalian target of rapamycin inhibitors

C. Azathioprine

D. Both B and C

03. A 52-year-old female who is hemodialysis dependent for 3 years wishes to switch to your dialysis unit because she believes that her unit is old and needs to be updated. She complains that she develops frequent headaches associated with nausea towards the end of dialysis treatments at her dialysis unit and believes that this may be due to carbon monoxide poisoning at the unit. She also complains that her dialysis unit kept harassing her about following strict fluid and dietary restrictions.
Investigation into which one of the following may BEST help uncover the reason for her symptoms?

A. Dialyzer membrane composition

B. Interdialytic weight gain

C. Temperature of dialysate

D. Use of mannitol during dialysis treatments

04. Which one of the following is CORRECT regarding diuretic effects on renal reabsorption of magnesium?

A. Thiazide diuretic: ↑renal reabsorption of magnesium

B. Loop diuretic: no change in renal reabsorption of magnesium

C. Sodium glucose cotransporter 2 inhibitor: ↑renal reabsorption of magnesium

D. Epithelial sodium channel inhibitor (eg, amiloride): ↓renal reabsorption of magnesium

05. A 42-year-old female presents with the following findings on a kidney biopsy: Electron microscopy shows lamellation and/or basket weaving pattern of the glomerular basement membrane.

Which ONE of the following can be concluded from her skin biopsy?

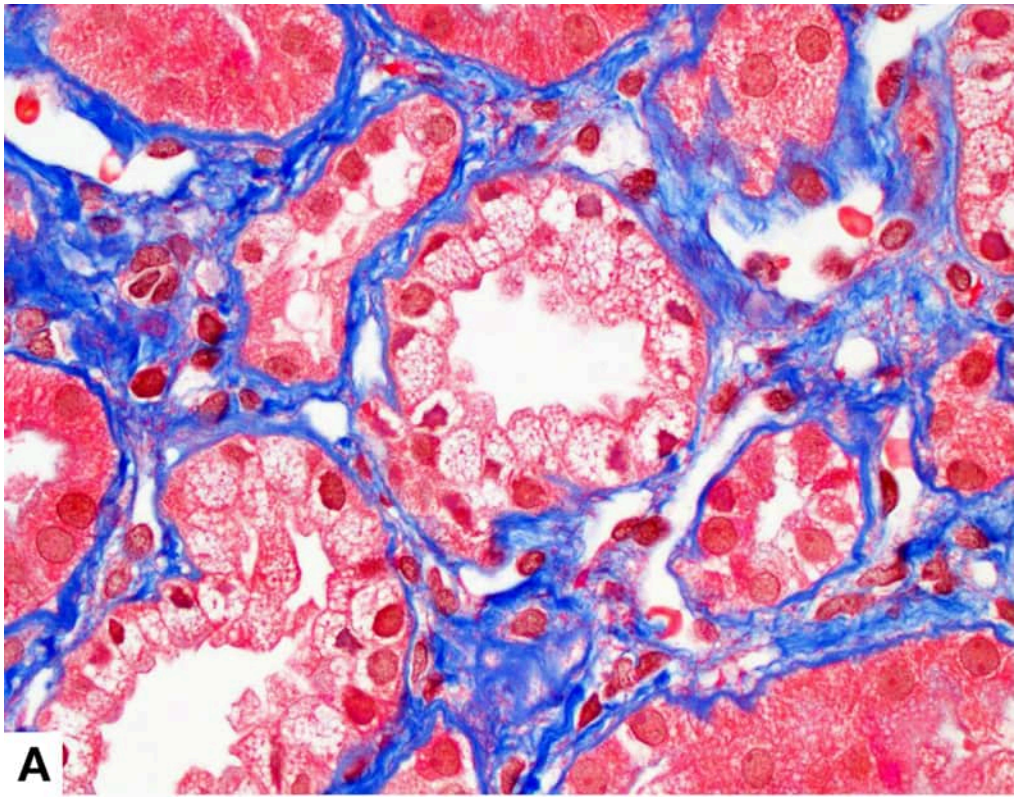
A. Absent or segmental staining for α5-type IV collagen chain suggests X-linked Alport syndrome (AS).
B. Normal staining for α5-type IV collagen chain rules out AS.
C. Absent or segmental staining for α3-type IV collagen chain suggests X-linked AS.
D. Absent or segmental staining for α3-type IV collagen chain suggests autosomal recessive AS.

06. A 48-year-old female with end stage kidney disease due to focal and segmental glomerulosclerosis, hemodialysis dependent over the past 2 months via a central venous catheter (CVC), presents with fevers and chills during her dialysis treatment. Routine blood cultures are drawn from both the CVC and peripheral vein, and the patient is immediately placed on empirical antibiotics. Three days following initiation of antibiotic therapy, blood cultures from both the CVC and peripheral vein are positive for *Staphylococcus epidermidis* susceptible to the current antibiotic regimen. However, the patient continues to have intermittent fevers. Hemodynamically, the patient remains stable and feels well. Which one of the following is the next BEST step?

A. Remove the current CVC and replace with a new CVC on a different day.
B. Exchange CVC over guidewire.
C. Continue the current antibiotic regimen.
D. Remove the current CVC and replace CVC at a different site at the same time.

07. A 64-year-old male with ESKD due to biopsy-proven diabetic nephropathy was admitted for deceased donor kidney transplant. He was on dialysis for 5 years, and his residual urine output was approximately 200 mL a day.
Admitting laboratory studies:
Creatinine 10.2 mg/dL

Hemoglobin 10 g/dL
HCT 30%
Urinalysis 2+ protein
CMV IgG Negative
EBV-viral capsid antigen (EBV-VCA) IgG Positive
EBV-nuclear antigen IgG Positive
Chest radiograph, ECG, recent cardiac stress test, and abdominal ultrasound were unremarkable.
The patient was cleared to proceed with kidney transplantation and was induced with antithymocyte globulin (ATG) due to prolonged cold ischemia time. His maintenance immunosuppression consists of tacrolimus, mycophenolate mofetil, and prednisone. He had slow graft function but did not require dialysis after transplant. After hospital discharge, he was seen in the clinic twice weekly for the first month after transplantation. At 1-month follow-up, his creatinine was 2.5 mg/dL (nadir since transplant). Urine protein creatinine ratio was 0.6. An allograft biopsy was performed due to persistently elevated baseline creatinine and proteinuria.



Trichrome stain 400×

Which one of the following is the MOST appropriate therapeutic option?

A. High-dose IV methylprednisolone pulse

B. Intravenous immunoglobulin (IVIG)

C. Tacrolimus to mTOR inhibitor switch

D. Tacrolimus to belatacept switch

08. A 32-year-old female presents to your clinic to establish long-term care. She has a history of 2,8-dihydroxyadenine (2,8-DHA) stone. She runs out of her "stone medication" but does not recall the name of the medication.

Which one of the following is the MOST likely medication used to treat 2,8-DHA stone?

A. Potassium citrate

B. Sodium citrate

C. Chlorthalidone

D. Allopurinol

09. A 50-year-old healthy African American male came to you for advice regarding living kidney donation. He should be informed of the following:

A. Apolipoprotein L1 (APOL1) genetic testing may be considered in African American living donor candidates with risk factors for the development of end stage kidney disease.

B. All prospective African American living donors should undergo APOL1 genetic testing for risk stratification.

C. The presence of two APOL1 risk variants is a contraindication to living donation.

D. Recipients should be informed of the donor's APOL1 genotype because it may impact the recipient's outcome.

10. A 38-year-old male with ESKD secondary to focal segmental glomerulosclerosis (FSGS) received a living donor–related kidney transplant from his mother 9 months ago. He had good graft function with baseline creatinine of 1.0 to 1.2 mg/dL. His maintenance immunosuppression consists of tacrolimus, mycophenolate mofetil, and prednisone. He was recently started on fluconazole for fungal urinary tract infection and pantoprazole/amoxicillin/clarithromycin triple-drug regimen for *Helicobacter pylori* infection. He did well until 5 days ago when he developed watery diarrhea with up to 10 bowel movements a day, associated with abdominal cramping. He denies nausea or vomiting. He denies chills or fever at home. On examination, his vital signs are as follows: temperature 37 °C (98.6 °F), BP 118/66, and respiratory rate 20. Cardiopulmonary examination is unremarkable, and there is no peripheral edema. The abdomen is soft, nondistended, nontender; bowel sounds are slightly hyperactive. There is no graft swelling or tenderness.
Laboratory studies:
Serum sodium 131 mmol/L, potassium 5.8 mmol/L, chloride 96 mmol/L, creatinine 1.9 mg/dL
Tacrolimus trough level 28 ng/mL

All of the following can lead to supratherapeutic tacrolimus level EXCEPT:

A. Diarrhea

B. Fluconazole

C. Pantoprazole/amoxicillin/clarithromycin combination therapy

D. All of the above

11. A 54-year-old male with no past medical history is admitted for evaluation of abdominal pain. The patient denies having any underlying medical history or taking any prescribed, herbal, or recreational drugs.
With the exception of diffuse abdominal tenderness, physical examination is otherwise unremarkable.
Laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	14.2	4-10 × 10^3/mL
Hemoglobin	8.5	Male: 14-17 g/dL
Hematocrit	25.3	Male: 45%-52%
Platelet count	404	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	130	136-145 mmol/L
Potassium	6.3	3.5-5.0 mmol/L
Chloride	97	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	27	8-20 mg/dL

Hematology	Patient	Reference range
Creatinine	1.6	0.7-1.3 mg/dL
eGFR (CKD-EPI 2021)	51	mL/min/1.73 m^2
Glucose (fasting)	89	70-100 mg/dL
Calcium	5.4	8.5-10.2 mg/dL
Albumin	3.6	3.5-5.5 g/dL

What is the next BEST step?

A. Redraw blood sample for repeat chemistry.

B. Obtain electrocardiogram.

C. Administer insulin and 50% dextrose.

D. Start sodium bicarbonate infusion.

12. A 31-year-old female with a history of end-stage kidney failure from autosomal recessive Alport syndrome presents for surgical peritoneal catheter placement. She is a newly graduated law student who is just accepted into a prestigious law firm. She is very excited about her job and wants to be informed about her peritoneal dialysis (PD) schedule. Her eGFR is 6.2 mL/min/1.73 m^2, and her daily urine volume still ranges between 1,000 and 1,500 mL.
Which one of the following initial PD prescriptions would work BEST for this patient?

A. Continuous ambulatory PD (CAPD), starting with 2 daytime dwells at 1,200 mL

B. Automated PD (APD), with 2 to 3 cycles, 1,200 mL dwell, over 6 to 7 hours total

C. APD, with 2 to 3 cycles, 1,500 mL dwell, over 6 to 7 hours total at nighttime and 1 daytime dwell

D. CAPD, starting with 2 daytime dwells at 1,200 mL, and one nighttime dwell

13. A 67-year-old male with a history of type 2 diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and end stage kidney disease and dialysis dependent is admitted for wet gangrene of the right foot. Vital signs are notable for hypotension, tachycardia, and high fevers. The patient reports increased fatigue and intermittent diarrhea over the past 2 weeks. Upon hospitalization, the patient was initiated on broad antibiotics including piperacillin/tazobactam and vancomycin, followed by right foot amputation. Over the next few days, the patient has worsening of his watery diarrhea associated with diffuse abdominal distention and tenderness. Abdominal examination reveals hypoactive bowel sounds. You are consulted for severe hypokalemia despite repeated infusions of large doses of potassium.
Medications: sevelamer, calcitriol, losartan, amlodipine, omeprazole, piperacillin/tazobactam, and vancomycin
Predialysis laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	9.2	4-10 × 10^3/mL
Hemoglobin	8.5	Male: 14-17 g/dL
Hematocrit	25.6	Male: 45%-52%
Platelet count	421	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	130	136-145 mmol/L
Potassium	[a]2.8	3.5-5.0 mmol/L
Chloride	95	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L

Hematology	Patient	Reference range
Anion gap	14	10-14 mmol/L
Blood urea nitrogen	54	8-20 mg/dL
Creatinine	4.3	0.7-1.3 mg/dL
Glucose (fasting)	89	70-100 mg/dL
Calcium	8.4	8.5-10.2 mg/dL
Magnesium	1.7	1.6-2.5 mg/dL
Albumin	2.7	3.5-5.5 g/dL

[a]Admission potassium was 4.0 mmol/L.

Nucleic acid amplification test (NAAT) for *Clostridium difficile* toxin gene is negative.
Liver function tests and lipase are within normal range.
Which one of the following is the next BEST diagnostic step?

A. Send stools for ova and parasites.
B. Discontinue antibiotics.
C. Obtain abdominal plain radiograph.
D. Provide a trial of pancrelipase (Pancreaze).

14. Focal and segmental glomerulosclerosis may arise from genetic inheritance or predisposition. Which one of the following statements is/are TRUE regarding genetic inheritance/predisposition to FSGS?

A. The presence of apolipoprotein L1 (APOL1) risk polymorphisms is a contraindication for a trial of glucocorticoid therapy.
B. Genetic FSGS is always associated with greater than 80% podocyte effacement.
C. Inheritance of two polymorphic risk alleles (G1, G2) of the *APOL1* gene increases the risk of FSGS, as well as the risk of progressive functional decline in patients with nondiabetic kidney diseases.

D. APOL1 polymorphisms protect against malaria.

15. A 49-year-old female with kidney failure of unknown etiology, requiring automated peritoneal dialysis, composed of four 2 L exchanges with 2.5% dextrose solutions over 8 hours and one 1.5 L daytime dwell with icodextrin, presents with worsening edema and weight gain despite adherence to her peritoneal dialysisregimen and dietary restrictions. She denies any history of constipation. A trial of tubing irrigation with added heparin did not result in any improved ultrafiltration.
Physical examination reveals 2+ edema up to knees bilaterally and weight gain of 4 kg since her last clinic appointment 4 weeks prior. Her two-dimensional echocardiography from 2 months ago revealed normal ejection fraction and diastolic function without any significant valvular abnormality.
Her daily urine output ranges between 200 and 300 mL, which is maintained with the use of bumetanide 3 mg and metolazone 5 mg bid.
What is the next BEST step?

A. Provide a 4.25% dextrose exchange challenge over 4 hours.

B. Increase the frequency of bumetanide and metolazone to tid.

C. Repeat her two-dimensional echocardiogram.

D. Switch to hemodialysis.

16. A 57-year-old male weighing 75 kg with a history of type 2 diabetes mellitus, hypertension, and hyperlipidemia presents with a history of recurrent uric acid stones. He endorses adherence to keeping a high fluid, low-sodium, and low-animal protein diet.
Current medications: insulin, amlodipine, losartan, atorvastatin

Hematology	Patient	Reference range
White blood cell count	5.7	4-10 × 10^3/mL
Hemoglobin	11.8	Male: 14-17 g/dL
Hematocrit	35.2	Male: 45%-52%

Hematology	Patient	Reference range
Platelet count	217	150-350 × 10^3/mL
Mean corpuscular volume	85	80-100 fL
Reticulocyte count	0.7	0.5%-1.5% of erythrocytes
Haptoglobin	215	50-220 mg/dL
Serum chemistry		
Sodium	133	136-145 mmol/L
Potassium	3.5	3.5-5.0 mmol/L
Chloride	91	98-106 mmol/L
Total CO_2 (bicarbonate)	30	23-28 mmol/L
Anion gap	12	10-14 mmol/L
Blood urea nitrogen	13	8-20 mg/dL
Creatinine	0.7	0.7-1.3 mg/dL
Glucose (fasting)	72	70-100 mg/dL
Calcium	9.7	9-10.5 mg/dL
Phosphorus	2.9	3-4.5 mg/dL
Magnesium	1.5	1.5-2.4 mg/dL
Uric acid	5.4	3.5-7.2 mg/dL
24-h urine metabolic profile		
Creatinine	1,890	Male: 20-25 mg/kg/24 h
Volume	2,700	L (variable)
pH	5.5	Variable

Hematology	Patient	Reference range
Calcium	156	Male: <250 mg/24 h
Uric acid	740	Male: <800 mg/24 h
Oxalate	33	<40 mg/24 h
Citrate	476	≥450 mg/24 h
Phosphorus	576	Male: 390-1,425 mg/24 h
Sodium	100	mmol (variable)

Which one of the following is the BEST preventive step against further stone growth?

A. Start potassium citrate.

B. Start febuxostat.

C. Start allopurinol.

D. Both A and B are correct.

17. A 29-year-old male with a history of unprovoked left lower extremity deep vein thrombosis and bilateral testicular hydrocele presents with a 4-week history of generalized lower abdominal pain. The pain is described as a constant ache, without any associated nausea/vomiting, diarrhea, melena, or hematochezia. He denies weight loss or any urinary symptoms.
Medication: apixaban
Physical examination: ill appearing
Vital signs: weight 78 kg, BP 120/70 mm Hg, pulse 76/min, respiratory rate 16/min, temperature 37.2 °C
Oropharynx: moist oral mucosa
Lungs: clear to auscultation bilaterally
Heart: normal S_1, S_2, no rubs or gallops
Abdomen: normal bowel sounds, soft, nondistended, mildly tender lower half abdomen without rebound or guarding, no hepatomegaly
Extremities: trace edema

Neurologic examination: nonfocal
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	133	136-145 mmol/L
Potassium	5	3.5-5.0 mmol/L
Chloride	97	98-106 mmol/L
Total CO_2 (bicarbonate)	18	23-28 mmol/L
Anion gap	18	10-14 mmol/L
Blood urea nitrogen	87	8-20 mg/dL
Creatinine	12 (1.1, 2 mo prior)	0.7-1.3 mg/dL
Glucose (fasting)	98	70-100 mg/dL
Calcium	9.2	9-10.5 mg/dL
Phosphorus	6.6	3-4.5 mg/dL
Magnesium	2.1	1.5-2.4 mg/dL
Urinalysis	**Patient**	**Normal range**
Color	Yellow	Yellow
Clarity/turbidity	Clear	Clear
pH	8.0	4.5-8.0
Specific gravity	1.014	1.005-1.025
Glucose	100 mg/dL	Negative
Ketones	Positive	Negative
Nitrites	Negative	Negative

Serum chemistry	Patient	Normal range
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilirubin	0.5	0.5-1.0 mg/dL
Blood	Negative	Negative
Protein	100 mg/dL	Negative
Red blood cells (RBCs)	0-2	≤2 RBCs/High power field (HPF)
White blood cells (WBCs)	0-5	≤2-5 WBCs/HPF
Squamous epithelial cells	None	<15-20 squamous epithelial cells/HPF
Casts	None	None

Urine protein to creatinine 1.21 g/g, urine albumin to creatinine 0.25 g/g, serum and urine protein electrophoresis and serum κ/λ are negative.

Abdominal and pelvic CT with intravenous contrast revealed mild bilateral hydroureteronephrosis and an ill-defined, infiltrative soft tissue mass encasing both the aorta and the inferior vena cava (~6.9 cm) and infiltrate along bilateral proximal common iliac vessels. Biopsy of the retroperitoneal mass shows dense fibroadipose tissue with lymphocytic aggregates, more than 50% IgG4-positive plasma cells, and fibrin deposition.

Which one of the following may MOST likely be found on this patient's kidney biopsy?

A. Interstitial fibrosis in a storiform (whirling) pattern

B. Focal and segmental glomerulosclerosis, collapsing variant

C. Light chain cast nephropathy, also known as myeloma kidney

D. Lupus nephritis class I or II

18. A 50-year-old male with a history of end stage kidney disease due to membranous nephropathy requiring automated peritoneal dialysis presents with severe and diffuse abdominal pain, fevers, and chills. As the patient's abdomen is empty, 1.5 L of 1.5% dextrose is infused. One hour after the fill, a sample from the peritoneal fluid is obtained and sent to the lab for cell count and cultures. The peritoneal fluid is slightly cloudy, but not bloody. White blood cell count (WBC) count is 75 WBCs/μL with 75% polymorphonuclear leukocytes (PMNs).
    Which one of the following statements is CORRECT?
    A. Streptococcal peritonitis may present with severe abdominal pain.
    B. The patient does not meet the criteria for peritonitis.
    C. Sampling of peritoneal fluid for cell count and culture is best done within 30 minutes of fill.
    D. Having greater than 100 WBCs/μL is likely a better indicator for peritonitis than having greater than 50% PMNs.
19. Which one of the following statements is CORRECT regarding diuretics?
    A. Loop diuretics also have a vasodilatory effect that may contribute to hypotension.
    B. Thiazide diuretics should be avoided in individuals with high risk for osteoporosis.
    C. The synergistic diuretic effect of a thiazide diuretic (eg, metolazone) and a loop diuretic is only effective when thiazide is administered 30 minutes prior to the administration of the loop diuretic.
    D. The use of sodium glucose cotransporter 2 inhibitors is associated with hyperuricemia.
20. Patients with chronic kidney disease (CKD) are at increased risk for extraosseous and vascular calcifications and cardiovascular events.
    Which one of the following statements is CORRECT?

A. Medial calcifications of arteries portend worse survival than intimal calcifications.

B. Denosumab may be protective against coronary artery calcification and beneficial to increasing bone density.

C. Denosumab is contraindicated in patients with CKD, ≥stage G4.

D. Compared with intimal and medial calcifications, adventitial calcification of arteries is associated with the worst survival risk.

21. A 64-year-old male being treated with nivolumab (anti–PD-1 antibody) and ipilimumab (cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] antibody) for malignant pleural mesothelioma presents with sudden-onset bilateral lower extremity edema. His other medication is acetaminophen.
Routine evaluation reveals hypoalbuminemia of 2.0 g/dL, urine protein to creatinine ratio of 15 g/g, predominantly albuminuria, and trace to 1+ glucosuria.
Which one of the following is the MOST likely diagnosis?

A. Acute interstitial nephritis (AIN)

B. Minimal change disease

C. IgG4-related disease

D. Podocytopathy and AIN

22. The patient is a 61-year-old male with ESKD secondary to atypical HUS (aHUS) associated with factor H mutation. He underwent a deceased donor kidney 7 days ago. Immunologic profile at the time of transplant: class I cPRA 60%, class 2 cPRA 70%. No donor specific antibody (DSA) was detected. He was induced with antithymocyte globulin (ATG) and maintained on tacrolimus, mycophenolate mofetil, and prednisone triple immunosuppressive therapy. His postoperative course was complicated by delayed graft dysfunction, oliguria, and worsening anemia and thrombocytopenia.
Laboratory studies:

	POD 1	POD 4	Units
SCr	8.7	8.5	mg/dL
WBC count	9.5	3.1	10^3/μL
Hemoglobin	9.1	6.7	g/dL
Hematocrit	27.3	20.1	%
Platelet count	175	17	10^3/μL
Lactate dehydrogenase	700	1,700	U/L
[a]Tacrolimus level	<0.5	4	ng/mL

[a]Reference range 10 to 12 ng/mL for the first 3 months after transplant.

ADAMTS13 activity: 85% (reference range 50%-150%)
Direct antiglobulin test: negative
Peripheral smear: anisocytosis, polychromasia, significant burr cells, 1 to 4 schistocytes/HPF, no platelet clumping, occasional large platelet
Differential diagnosis may include:

A. Acute antibody-mediated rejection
B. Recurrent aHUS
C. Thrombotic thrombocytopenic purpura (TTP)
D. All of the above

23. A 62-year-old male with a history of end stage kidney disease due to diabetic kidney disease requiring hemodialysis support for over 10 years complains of slowly progressive numbness and prickling sensations and increased pain sensation starting in both legs, which have now also involved upper arms, followed by frequent muscle cramps, relieved with leg movement, and bilateral lower extremity weakness. Physical examination is notable for orthostatic hypotension, sensory deficits to temperature, pinprick, and vibration in distal extremities, bilateral muscle weakness, and diffuse hyporeflexia. Cognitive function is intact. Laboratory

studies reveal hemoglobin A1C of 6.2%, normal thyroid function, parathyroid hormone 175 pg/mL, electrolytes (sodium, potassium, calcium, magnesium, phosphorus) within normal limits, blood urea nitrogen 45 mg/dL, creatinine 3.7 mg/dL, and hemoglobin 12 g/dL with mean corpuscular volume 85 fL.
Which one of the following is the MOST likely diagnosis?

A. Diabetic polyneuropathy

B. B_{12} deficiency

C. Restless leg syndrome (RLS)

D. Uremic polyneuropathy (UPN)

24. A 42-year-old male with a history of HTN initially present to the emergency department for a 3-month history of gradual worsening of bilateral lower extremity edema followed by back pain during the last week. Blood and urine studies were consistent with NS. Abdominal and pelvic CT revealed a large, elongated clot within the inferior vena cava extending from the hepatic vein to the level of the kidneys. A kidney biopsy performed was consistent with antiphospholipase A2 receptor antibody–positive MN. Hypercoagulability and underlying malignancy evaluations were negative. The patient was treated with lisinopril and one dose of RTX and discharged. The patient was lost to follow-up and returns 2 months later with the following laboratory studies:

	2 mo ago	Now	Reference range
Sodium	142	138	136-145
Potassium	3.9	3.5	3.5-5.0
Chloride	111	101	98-106
Total CO_2	21	26	23-28
Blood urea nitrogen	25	19	8-20

	2 mo ago	Now	Reference range
Creatinine	1.16	1.62	0.5-1.1
eGFR	80 mL/min/1.73 m^2	54 mL/min/1.73 m^2	≥90 mL/min/1.73 m^2
Glucose	80	95	70-99, fasting
Albumin	2.2	1.9	3.5-4.8
uPCR	8.9 mg/mg	10.6 mg/mg	<0.2
Antiphospholipase A2 receptor antibody	Positive 71 RU/mL	Positive 31 RU/mL	Negative

What is the next BEST therapeutic option for this patient?

A. Cyclophosphamide plus GCs

B. Tacrolimus

C. RTX

D. Continue supportive treatment with lisinopril and BP control.

25. A 37-year-old female with a history of lupus nephritis class III + V is admitted for total body pain and pleuritic chest pain. Initial evaluation suggests active lupus flare with associated pericarditis, myositis, and acute kidney failure. Patient rapidly deteriorates and requires mechanical ventilation. She is placed on a loop diuretic drip with urine output ranging from 50 to 75 mL/h. The young intensivist asks for your opinion regarding fluid balance goal. Which one of the following statements is CORRECT regarding fluid status and outcome in critically ill patients?

A. Patients should be kept euvolemic to slightly hypervolemic to ensure good renal perfusion and renal recovery.

B. Euvolemic and slightly hypervolemic patients have been shown to have improved survival benefit.

C. Available data suggest that volume overload may delay the diagnosis of acute kidney injury and is associated with worse outcomes.

D. Volume overload is associated with delayed AKI diagnosis, but not with outcomes.

26. A 62-year-old female with a history of diabetes, hypertension, and hyperlipidemia presents to the general nephrology clinic for worsening leg edema for 2 months.
At the current clinic visit, her BP is 128/72 mm Hg and pulse is 72 beats per minute. Physical examination is notable for 3+ edema bilaterally. Urinalysis in only notable for greater than 300 mg/dL protein and urine protein to creatinine is 5.2 g/g. Serum creatinine is 1.0 mg/dL. Proteinuria evaluation including complements C3, C4, CH50, HIV, rapid plasma reagin, acute hepatitis panel, serum and urine protein electrophoresis, serum κ/λ levels, antinuclear antibody, and anti–double-stranded DNA antibody are negative. Antiphospholipase A2 receptor antibody is highly positive. Kidney ultrasound reveals normal-sized kidneys without any structural abnormality.
While providing patient supportive therapy, which ONE of the following step(s) remain(s) to be done?

A. ANCA titer

B. Malignancy screen appropriate for age, gender, and personal risks

C. Anti-glomerular basement membrane

D. All of the above

27. A 59-year-old male with septic shock is admitted to the ICU. After intravenous fluid resuscitation, he requires norepinephrine and vasopressin to improve his mean arterial pressure to 70 mm Hg and develops oliguric acute kidney injury. On examination, he is intubated and sedated. Anasarca is present, and there are coarse breath sounds over both lung fields.
Laboratory studies:

Serum chemistry	At presentation	12 h post CKRT	Reference range
Sodium	134	137	136-145 mmol/L
Potassium	5.7	3.8	3.5-5.0 mmol/L
Chloride	102	98	98-106 mmol/L
Total CO_2 (bicarbonate)	20	18	23-28 mmol/L
Anion gap	12	21	10-14 mmol/L
Blood urea nitrogen	84	30	8-20 mg/dL
Creatinine	3.2	2.1	0.7-1.3 mg/dL
Albumin	3.6	3.6	3.5-5.5 g/dL
Total calcium	2.28	2.6	2.2-2.7 mmol/L
Ionized calcium	1.25	0.975	1.16-1.31 mmol/L
Lactic acid	6	8	<2 mmol/L

Continuous kidney replacement therapy (CKRT) is begun using citrate anticoagulation. CaCl is infused through the return line at 60 mL/h.
Laboratory studies obtained 12 hours later are shown in table.
CaCl infusion rate has been increased to 80 mL/h.
Which one of the following is MOST consistent with citrate accumulation in this patient?

A. The calcium corrected for the serum albumin

B. Worsening metabolic acidosis

C. The ratio of the total calcium to ionized calcium

D. Decreasing systemic ionized calcium level

28. Which one of the following statements is CORRECT regarding urine alkalinization in the treatment of kidney stones?

A. Risk of triple phosphate stone (commonly referred to as "struvite stone") formation may increase.

B. Sodium citrate is generally preferred to potassium citrate.

C. Risk of calcium oxalate stone may increase.

D. Risk of calcium phosphate stone may increase.

29. A 43-year-old male with a history of depression, hypertension, and deceased donor kidney transplant due to end stage kidney disease from congenital renal hypoplasia presents for routine follow-up.
Medications: tacrolimus, venlafaxine, prednisone, mycophenolate mofetil, amlodipine
Laboratory studies:

Serum chemistry	Patient	Normal range
Sodium	140	136-145 mmol/L
Potassium	5.2	3.5-5.0 mmol/L
Chloride	107	98-106 mmol/L
Total CO_2 (bicarbonate)	21	23-28 mmol/L
Blood urea nitrogen	12	8-20 mg/dL
Creatinine	0.8	0.7-1.3 mg/dL
Glucose (fasting)	97	70-100 mg/dL
Calcium	9.4	9-10.5 mg/dL
Phosphorus	4.0	3-4.5 mg/dL
Magnesium	1.8	1.5-2.4 mg/dL

Urinalysis is noted for 1+ proteinuria without glucosuria, cells, or casts.
Which one of the following medications is the MOST likely contributor to his HTN based on the presenting chemistry?

A. Prednisone

B. Tacrolimus

C. Venlafaxine

D. Mycophenolate mofetil

30. A 67-year-old female with end stage kidney disease (ESKD) requiring peritoneal dialysis support for 4 years presents with bone pain and easy fractures. A bone biopsy reveals low bone turnover and poor osteoid matrix consistent with adynamic bone disease (ABD).
Which one of the following biochemical profiles is MOST consistent with ABD in a patient with ESKD requiring kidney replacement therapy?

	PTH	Serum calcium	Serum phosphorus	Bone-specific alkaline phosphatase
A.	High	Low	High	High
B.	Normal to high	Low	High	Normal to low
C.	Normal to low	High	Normal to low	Normal to low
D.	Low	Normal to low	Low	Normal to high

31. A 32-year-old female with a history of malar rash presents with anemia, thrombocytopenia, proteinuria of 3.5 g/g creatinine, and rising serum creatinine The patient undergoes a kidney biopsy that is complicated by a moderately large capsular hematoma.
Which one of the following may MOST likely result from the capsular hematoma?

A. Hypertension

B. Erythrocytosis

C. Hypotension

D. Bradycardia

32. A 27-year-old male with a history of frequent relapsing MCD since age 10 presents to a clinic for follow-up. One month prior, the

patient was given prednisone 60 mg daily when he presented for a relapse. At the current visit, the patient reports improved lower extremity edema. However, it is noted that the patient has had significant weight gain over the years, increasing blood glucose levels with the most recent hemoglobin A1C at 6.8% despite healthy lifestyle and dietary modifications, and presumed steroid-induced acne and abdominal bloating. Upper endoscopy and colonoscopy previously performed were without abnormal findings. The patient plans to wed in 2 months and have children with his long-time fiancée.

In addition to prednisone, which of the following medications is the BEST option to treat his relapse?

A. Cyclophosphamide

B. Tacrolimus or cyclosporine

C. Mycophenolate mofetil

D. Rituximab

33. A 100-kg patient is on the following CKRT parameters:
Continuous venovenous hemodiafiltration
Blood flow 100 mL/min
Prefilter replacement fluid 1,800 mL/h
Dialysate 1,000 mL/h
Postfilter RF 200 mL/h
Fluid removal 250 mL/h
Hematocrit 25%
What is the continuous kidney replacement therapy prescribed dose?

A. 19 mL/kg/h

B. 28 mL/kg/h

C. 33 mL/kg/h

D. 49 mL/kg/h

34. A 26-year-old male with end stage kidney disease secondary to posterior urethral valve received a deceased donor kidney 2 years ago. His maintenance immunosuppression consisted of

tacrolimus, mycophenolate mofetil, and prednisone. He was lost to follow-up for almost 1 year until 3 days ago when he presented to the emergency department with nausea, vomiting, metallic taste, difficulty concentrating, decreased urine output, fever, and pain over the allograft. His home medications include mycophenolate mofetil, prednisone, carvedilol, and losartan. He admitted to stopping tacrolimus 4 months ago because he felt well. His vital signs show temperature of 38 °C (100.4 °F), BP 160/89 mm Hg, and pulse 82 beats per minute. Physical examination is notable for allograft swelling and tenderness, and 1+ peripheral edema. Lungs are clear to auscultation.
Pertinent laboratory studies:

Hematology	**Patient**	**Reference range**
WBC count	8.2	4-10 × 10^3/mL
Hemoglobin	8.9	Male: 14-17 g/dL
Hematocrit	28.4	Male: 45%-52%
Platelet count	214	150-350 × 10^3/mL
Mean corpuscular volume	87	80-100 fL
Serum chemistry		
Sodium	133	136-145 mmol/L
Potassium	6.5	3.5-5.0 mmol/L
Chloride	94	98-106 mmol/L
Total CO_2 (bicarbonate)	19	23-28 mmol/L
Anion gap	20	10-14 mmol/L
Blood urea nitrogen	118	8-20 mg/dL
Creatinine	11.2	0.7-1.3 mg/dL

Hematology	Patient	Reference range
Glucose (fasting)	98	70-100 mg/dL

Urinalysis is notable for 2+ protein.
Urine and blood cultures are negative.
Chest radiograph shows no cardiopulmonary findings.
Which one of the following is the MOST appropriate management strategy?

A. Allograft biopsy to rule out acute rejection in the setting of medical nonadherence
B. Reinitiate dialysis, high-dose methylprednisolone pulse
C. Conservative medical management (sodium zirconium cyclosilicate and high-dose loop diuretics), allograft biopsy
D. Broad-spectrum antibiotic therapy, initiate dialysis for hyperkalemia, allograft biopsy

35. A 36-year-old female with a history of systemic lupus erythematosus and body mass index of 32 kg/m^2 presents for routine prenatal care at gestational age 15 weeks. Her office blood pressure is in range with her ambulatory blood pressure, which are in the systolic range of 140 to 160 mm Hg and diastolic range of 80 to 95 mm Hg. She is currently not taking any medication, except for one prenatal vitamin daily.
Which one of the following would BEST reduce her risk of preeclampsia?

A. Continuation of hydroxychloroquine
B. Initiation of low-dose aspirin prior to 16 weeks and continue for the duration of pregnancy
C. Initiation of sodium glucose cotransporter 2 inhibitor
D. Initiation of thiazide diuretic

36. A 43-year-old male recently diagnosed with autosomal dominant polycystic kidney disease arising from polycystin 2 mutation by genetic testing is referred for tolvaptan therapy. He has multiple

cysts in his right kidney, with total length measuring 17 cm, but none in his left kidney. His current eGFR is 45 mL/min/1.73 m^2.
Which ONE of the following conditions precludes him from tolvaptan therapy due to unknown risk/benefit ratio?

A. eGFR

B. Age

C. Unilateral disease

D. Polycystin 2 mutation

37. A 50-kg patient is placed on continuous venovenous hemofiltration with postfilter replacement fluid (RF) rate at 1,000 mL/h. Serum potassium is 6.0 mEq/L. The concentration of potassium in the RF is 2 mEq/L.
How much more potassium is lost in the effluent by increasing the effluent dose from 20 to 35 mL/kg/h?

A. 3 mEq/h

B. 5 mEq/h

C. 7 mEq/h

D. 9 mEq/h

38. A 55-year-old female with a history of ANCA-associated glomerulonephritis, lost to follow-up for 3 years, on no medication, now presents to reestablish care.

Serum chemistry	Patient	Reference range
Sodium	133	136-145 mmol/L
Potassium	4.5	3.5-5.0 mmol/L
Chloride	91	98-106 mmol/L
Total CO_2 (bicarbonate)	22	23-28 mmol/L
Anion gap	20	10-14 mmol/L
Blood urea nitrogen	70	8-20 mg/dL
Creatinine	5.4	0.7-1.3 mg/dL

Serum chemistry	Patient	Reference range
Glucose (fasting)	99	70-100 mg/dL
Total calcium	10.7	8.5-10.2 mg/dL
Phosphorus	2.8	2.8-4.5 mg/dL
Albumin	3.1	3.5-5.5 g/dL
Alkaline phosphatase	171	44-147
Parathyroid hormone	256	10-65 pg/mL

Which one of the following is the next BEST step?

A. Perform bone biopsy.

B. Prescribe a calcium-sensing receptor agonist.

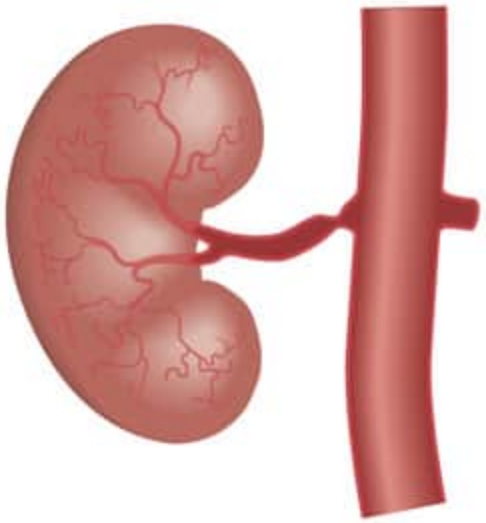
C. Refer to otolaryngology for parathyroidectomy evaluation.

D. Obtain parathyroid scan.

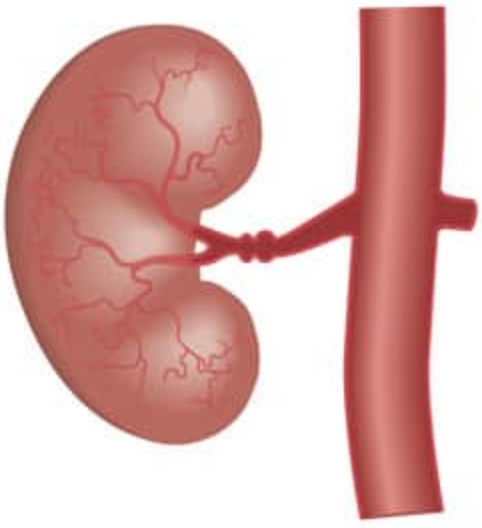
39. A 27-year-old female with a history of hypertension presents with anorexia, weight loss of 4 kg over the past 3 months, subjective fevers, colicky abdominal pain (often postprandial), and multiple ulcerated lesions in thighs and legs. Review of system is notable for a history of burning sensation in both feet and joint pains over the past 1 to 2 years and an episode of melanotic stool 6 months ago.
Physical examination: thin pale female, chronically ill appearing
Vital signs: BP 170/100 mm Hg, pulse 86/min, respiratory rate 16/min, temperature 37.2 °C
Neck: no lymphadenopathy, no bruits, no jugular vein distention
Oropharynx: within normal limits with moist oral mucosa
Lungs: clear to auscultation
Heart: regular rate, hyperdynamic heart sounds, no murmurs, gallops, rubs
Abdomen: moderate distention, hypoactive bowel sounds, mild tenderness with palpation, no rebound or guarding, +hepatosplenomegaly, +fluid shift

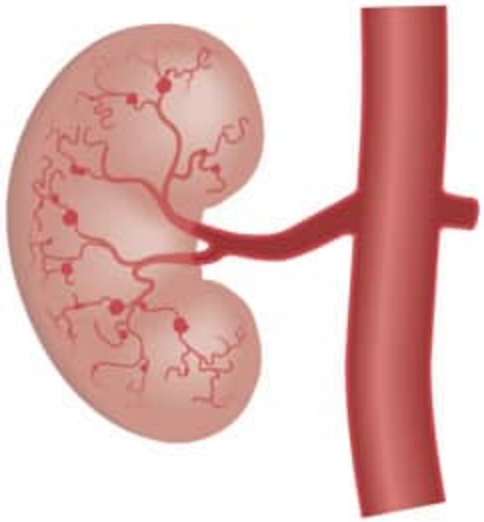
Extremities: asymmetric swollen proximal and distal interphalangeal joints, hyperpigmented bilateral feet, multiple ulcerated lesions at different stages of healing, reduced pulses in dorsalis pedis and tibial arteries
Deep tendon reflexes: symmetric, 2+ throughout
Neurologic examination: nonfocal, except for hyperesthesia
Initial evaluation reveals iron deficiency anemia, hemoglobin 7.2 g/dL, elevated erythrocyte sedimentation rate, transaminitis, hyperbilirubinemia, prolonged INR of 3.7, and elevated SCr at 4.7 mg/dL. Skin biopsy reveals "leukocytoclastic vasculitis."
Which one of the following is the MOST likely finding on angiogram?

A.



B.





C.

D. None of the above

40. Absolute contraindications to kidney transplantation include all of the following EXCEPT:

A. Ongoing nonhealing ulcers

B. Compensated hepatitis C–associated liver cirrhosis

C. Limited, irreversible rehabilitation potential

D. Poorly controlled psychiatric illness

ANSWERS

1. **Answer:** A
   The patient has normal serum anion gap (SAG) metabolic acidosis with urine AG 72 + 33 − 80 = 25, which is greater than 0. A positive urine AG in the presence of a normal AG metabolic acidosis in a patient with relatively good kidney function suggests the presence of RTA. An associated low K^+ rules out distal RTA type 4. A urine pH of 6 is more consistent with distal RTA type 1. For proximal RTA type 2, the urine pH should be low, that is, 5.5 or less when serum bicarbonate is very low. In addition, proximal RTA type 2 is typically self-limited, where serum bicarbonate usually ranges 14 to 16 mmol/L, not severely low as seen in the current case.
2. **Answer:** D

The biopsy shows (A) glomerulus with global glomerulitis and (B) diffuse C4d peritubular capillary staining on immunofluorescence diagnostic of acute antibody-mediated rejection (AMR). IVIG with or without plasmapheresis is considered the standard of care for the treatment of acute AMR. Although the MFI threshold to perform plasmapheresis differs among centers, most clinicians advocate plasmapheresis in conjunction with IVIG therapy in patient who displays strong DSAs against class I and/or class II. De novo DSAs are frequently seen in the context of medical nonadherence or inadequate immunosuppression.

ATG is generally used for the treatment of acute T-cell–mediated rejection (TCMR) type II A or greater or in corticosteroid-refractory TCMR.

3. **Answer:** C

   Drug clearance by dialysis is considered clinically significant if drug clearance is increased by 30% or more with dialysis. Drug clearance may be increased in the setting of peritonitis due to increased blood flow. Protein-bound drugs may be better cleared with PD compared with HD due to larger peritoneal membrane pore size.

4. **Answer:** B

   A female patient with X-linked AS carries one normal allele. Because of this, the normal noncollagenous domain of type IV collagen α5 chain is present throughout the patient's life and will not be identified as a foreign antigen in the allograft transplant kidney. Antibodies will not be formed against the normal noncollagenous domain of type IV collagen α5 chain in the allograft kidney.

5. **Answer:** C

   Targeted-release formulation of the GC budesonide is an agent that can be considered in patients with immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, defined as having uPCR greater than 1.5 g/g or proteinuria greater than 2 g/d, who cannot tolerate or do not wish to take systemic GCs.

Sparsentan is a dual angiotensin II receptor subtype 1 and endothelin type A receptor antagonist that was U.S. Food and Drug Administration (FDA) approved in February 2023 to treat patients with IgAN who are at risk for progression. It may be considered an alternative option to reduce proteinuria in patients with IgAN and persistent proteinuria 1 g/d or more despite optimal treatment with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) and sodium-glucose cotransporter 2 inhibitor (SGLT2i).

Avacopan is a complement 5a receptor antagonist and a cytochrome P450 3A4 (CYP3A4) inhibitor. Avacopan may be considered in place of GC for induction therapy in combination with either rituximab (RTX) or cyclophosphamide in patients with increased risk of GC toxicity (eg, high infection risk, diabetes mellitus [DM], psychiatric disorders, osteoporosis). In the ADVOCATE trial involving 330 patients with ANCA-associated vasculitis, 81% with renal involvement, eGFR improved by an average of 7.3 versus 4.1 mL/min/1.73 m^2 at 52 weeks in the avacopan versus prednisone group, respectively. In patients with eGFR 20 mL/min/1.73 m^2 or less, eGFR improved by 16.1 versus 7.7 mL/min/1.73 m^2 at 52 weeks with avacopan versus prednisone.

Methylprednisolone is a GC.

6. **Answer:** C

Calcineurin inhibitors (CNIs) (cyclosporine [CSA] and tacrolimus) are extensively metabolized by the CYP3A4 enzyme system in the liver; therefore, drugs that inhibit CYP3A4 enzyme or drugs that compete for its pathways will increase CSA and tacrolimus drug levels. Paxlovid contains nirmatrelvir and ritonavir. The latter is a potent CYP3A4 inhibitor; therefore, its use can result in significantly elevated tacrolimus level and CNI toxicity. Paxlovid should be avoided in patients receiving CNI therapy.

Grapefruit and pomegranate increase CNI level by increasing CNI absorption. Grapefruit and pomegranate may also inhibit CYP3A4 activity.

St John wort decreases CNI level by induction of CYPA4 activity.

7. **Answer:** D
   We only have one set of laboratory values without any definitive evidence for CKD, AKD, or AKI.
   Definition of AKI (from 2020 Controversies in AKI Kidney Disease Improving Global Outcomes [KDIGO] Conference)
   - Increase in SCr by more than 50% within 7 days, or
   - Increase in SCr by 0.3 mg/dL or more within 48 hours, or
   - Oliguria

   Definition of AKD
   Conditions of impaired kidney function not meeting criteria (in terms of severity and/or duration of kidney damage) for either AKI or CKD but with associated adverse outcomes requiring clinical care
   CKD definition (KDIGO)
   CKD is defined as having either structural or functional abnormalities of the kidneys, of 3 months or more in duration, with implications for health.
   Structural abnormalities of the kidney refer to either pathologic abnormalities on biopsy or imaging or markers of kidney damage, including abnormalities in the composition of the blood or urine (eg, may include abnormal serum or urine markers of tubular or glomerular dysfunction).
   Functional abnormality of the kidney refers to having GFR less than 60 mL/min/1.73 m^2 with or without underlying kidney damage (eg, hepatorenal or cardiorenal syndrome causing dysfunction related to decreased renal perfusion and may not be associated with fixed kidney damage).
   Chronicity is defined as a duration of 3 months or more or evidence of chronicity, for example, findings on imaging of decreased kidney size, atrophy, loss of cortical definition; presence of chronically low GFR; finding on biopsy of tubular atrophy, and tubulointerstitial fibrosis.

8. **Answer:** A

ISH occurs with stiffening of large arteries, leading to reduced vessel capacitance and acceleration of pulse wave velocity, hence widening of pulse pressure. Systolic blood pressure (SBP) in patients with ISH continues to increase throughout life.

IDH is defined as having diastolic blood pressure (DBP) 80 mm Hg or more with SBP less than 130 mm Hg. It is more common in young males who are overweight or obese. If no specific indication for any antihypertensive class, patients with IDH tend to respond well with just one agent, typically better with an ARB or ACEi than dihydropyridine calcium channel blocker (CCB).

Masked HTN refers to having lower office BP compared with that measured in the out-of-office setting. This is the opposite of WCH. Both masked HTN and WCH are associated with increased cardiovascular events. Treatment is indicated when there is evidence of end-organ damage (eg, left ventricular hypertrophy by electrocardiogram [ECG] or echocardiogram) or persistent office HTN for WCH or elevated ambulatory BP measurements for masked HTN.

9. **Answer:** B

   Clearance of the drug is still 30% by liver, but now clearance by kidneys is only 40% of 70%, which is 28%. Total drug clearance would now be 30% by liver plus 28% by kidneys, or 58% total clearance. Maintenance dose should be reduced to 58% of normal dose, 58 mg.

10. **Answer:** C

    This patient has unexplained worsening of kidney function. Physical examination is notable for significant pedal edema. Urinalysis is notable for hyaline casts and minimal microscopic hematuria. Although diabetic kidney disease can present with microscopic hematuria, evaluation for urologic abnormalities is normally warranted for persistent microscopic hematuria because the former is a diagnosis of exclusion. However, that option is not given in this question. The presence of hyaline casts should raise concerns for reduced renal perfusion. Given moist oral mucosa and significant pedal edema, holding furosemide is not a good

option. In this patient with multiple cardiac risk factors, reduced cardiac output resulting in renal hypoperfusion must be considered. A two-dimensional echocardiogram should be done to evaluate for any change in cardiac function, for example, new-onset reduced left ventricular function or cardiac output. Adding spironolactone is not a good option in patient who is developing rapid progression of kidney injury of unknown etiology. There is no clinical history or lab findings suggestive of obstructive uropathy (ie, difficulty voiding, hyperkalemia, metabolic acidosis out of proportion to the degree of kidney injury) to suspect a high postvoid residual volume.

11. **Answer:** A

    In granulomatous disease, the primary problem leading to hypercalcemia is increased 1α-hydroxylase activity in macrophages that converts 25(OH)-vitamin D to its active form $1,25(OH)_2$ vitamin D. The latter increases gut absorption of both calcium and phosphorus. Serum phosphorus may be normal to high depending on kidney function.

12. **Answer:** D

    Estimations of GFR using either SCr or cystatin c may be affected by non-GFR determinants; therefore, GFR estimate equations using both are generally more accurate than those using only one measure. GFR estimation using creatinine can be overestimated by the impact of tubular secretion of creatinine, whereas cystatin c is absorbed and metabolized by the renal tubules with (negligible) tubular reabsorption or secretion.

    Non-GFR determinants of GFR estimation using SCr can include relative muscle mass, dietary protein intake, and medications affecting tubular secretion. Those affecting GFR estimates using cystatin c include obesity, underlying inflammatory state, and thyroid disorders.

    A meta-analysis of 11 studies showed reclassification of a significant proportion of patients to a different CKD category using cystatin c versus SCr and found renal prognosis correlated with the new CKD category.

(Chen DC, Potok OA, Rifkin D, Estrella MM. Advantages, limitations, and clinical considerations in using cystatin C to estimate GFR. *Kidney360*. 2022;3[10]:1807-1814. doi:10.34067/KID.0003202022)

13. **Answer:** D
    The patient has normal AG metabolic acidosis with urine AG 22 + 33 − 100 = −45, which is less than 0. A negative urine AG in the presence of normal SAG metabolic acidosis suggests an extrarenal cause such as diarrhea or biliary drains. Autoimmune disease such as Sjögren disease may be associated with distal RTA type 1. Hypoaldosteronism is associated with distal RTA type 4. Fanconi syndrome is associated with proximal tubular injury and may be seen in some patients with proximal RTA. Option D evaluates for diarrhea.
14. **Answer:** C
    Living donation does not impact future fertility. Women with prior history of hypertensive disorders of pregnancy may be acceptable for donation if their long-term postdonation risks are acceptable (2017 KDIGO Clinical Practice Guidelines). Donation in individuals with or without a prior history of HTN may increase the risk of gestational HTN and preeclampsia. It may also increase the risk of hyperuricemia, gout, and hyperthyroidism.
15. **Answer:** B
    The low urine osmolality suggests poor oral intake and/or polydipsia. Poor oral intake resulting in "tea and toast" hyponatremia is less likely as she endorses eating well. The reason for this patient's hyponatremia is most likely polydipsia. Her polydipsia is most likely due to dry mouth from taking daily diphenhydramine. Referral to an allergy specialist is appropriate. It is important to treat the underlying source of polydipsia rather than just advising patients to drink less fluid.
    There is no evidence that the current patient has any psychiatric problem that would cause polydipsia as she is fully alert and oriented and answers to all questions appropriately. Physical

examination shows no evidence of hypothyroidism to consider hypothyroid-associated hyponatremia.

16. **Answer:** A
    The GFR equivalent is based on the continuous kidney replacement therapy (CKRT) clearance, which is = unbound drug fraction × effluent rate = 0.5 × 30 mL/kg/h × 100 kg = 1,500 mL/h or 1,500 mL/60 min = 25 mL/min. Therefore, dosing for the antibiotic should be equivalent to that given to a patient with a GFR (~creatinine clearance) of 25 mL/min.
17. **Answer:** D
    Metoprolol is dialyzable. There is evidence to suggest increased cardiovascular death in dialysis patients using dialyzable β-blockers compared to nondialyzable β-blockers. Metformin is dialyzable. The beneficial effect of HD in metformin-induced lactic acidosis lies more in correcting the acidosis rather than in removing metformin. KDIGO guidelines regarding the use of metformin in patients with CKD: Reduce dose if eGFR is less than 45 mL/min/1.73 m^2 and discontinue if eGFR less than 30 mL/min/1.73 m^2. Dabigatran is dialyzable but it has a large volume of distribution. For this reason, prolonged dialysis may be necessary to remove the drug. The beta-blockers carvedilol and labetalol are not dialyzable. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. *Am J Kidney Dis*. 2013;61(3):487-9.
18. **Answer:** D
    A high urine osmolality, that is, greater than 200 mOsm/kg suggests the presence of ADH or osmotic diuresis. Complete central DI is less likely because of the high urine osmolality and rapid drop in serum sodium concentration.
    Acute central DI should present with increasing serum sodium concentration.
    SIADH can only be diagnosed in a euvolemic patient. This patient has evidence of hypovolemia (dry oral mucosa). The high urine volume is also inconsistent with SIADH as water reabsorption

should be very effective. Patients with SIADH generally have relatively low urine output.

Adrenal insufficiency could be a problem, but the relatively normal serum potassium and low uric acid are not typical of adrenal insufficiency. In addition, the morning cortisol level is within normal limits.

CSW can present with hypovolemia due to salt wasting (urine sodium + potassium in current patient adds up to ~150 mmol/L) and low serum uric acid. CSW is most commonly reported among patients with subarachnoid hemorrhage.

19. **Answer:** B

Management of genetic FSGS

Patients with FSGS due to genetic mutations should be treated with inhibitors of the renin-angiotensin system, sodium restriction, BP control, and, possibly, bicarbonate, but not with immunosuppression.

APOL1: Patients with two APOL1 risk polymorphisms (G1/G1, G2/G2, G1/G2) should be treated the same as patients with primary FSGS. Consider referral to an APOL1 clinical trial for patients with suboptimal response to therapy. Phase 2 and 3 clinical trials are now underway to test whether inhibiting APOL1 transcription or signaling in patients with two risk variants will reduce proteinuria and preserve renal function in patients with FSGS or HTN.

Rare patients with mutations, such as those with coenzyme Q2 or Q6 mutations, may respond to specific therapies (in this case, coenzyme Q10).

Review of primary (idiopathic) FSGS (1° FSGS)

Primary FSGS: The recurrence of proteinuria and 1° FSGS following kidney transplantation, transient proteinuria in an infant born to a mother with 1° FSGS, and resolution of proteinuria in a retransplanted kidney from a recipient with 1° FSGS into a recipient without the condition all support the role of a circulating permeability factor in the pathogenesis of 1° FSGS.

Antinephrin antibodies have been implicated as pathogenic in up to two-thirds of children and adults with primary FSGS and may be viewed as one of the sought-after circulating permeability factors. Other circulating permeability factor candidates, including soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine-1, angiopoietin-like 4, and CD80, remain to be independently validated.

Although microscopic hematuria may be present in patients with FSGS, hematuria per se has not been reported to be a progression risk factor for FSGS. Collapsing FSGS is the most aggressive variant of primary FSGS, with Black racial predominance and severe NS portending worse prognosis. Patients with collapsing FSGS tend to have poor response to GC therapy.

20. **Answer:** B

Dolutegravir is metabolized primarily via hepatic glucuronidation by UGT1A1 with a small contribution from CYP3A4. It does not form long-lived metabolites. Dolutegravir may cause an increase in SCr without apparent decrease in renal function, thought to be due to inhibition of tubular secretion of creatinine via the organic cation transporter OCT2 (similar to the interaction seen with cimetidine or trimethoprim). All others produce metabolites that accumulate in patients with reduced kidney function: Allopurinol → oxypurinol (tubulointerstitial nephritis), morphine → morphine-3-glucuronide and morphine-6-glucuronide (altered mental status, seizures, respiratory depression), nitroprusside → thiocyanate (cyanide toxicity), venlafaxine → *O*-desmethylvenlafaxine (altered mental status).

21. **Answer:** A

HIVAN is only seen in patients with severe/advanced HIV (ie, CD4 <200 cells/mm^3, high viral load). Since the advent of effective combined antiretroviral therapy, HIVAN is rare. HIVICK is the most common form of kidney disease seen with HIV. These may include IgAN, lupus-like GN, membranous nephropathy (MN),

membranous/mesangial proliferative GN, postinfectious GN, and immunotactoid/fibrillary GN.

Tenofovir-associated Fanconi syndrome and acute tubular injury may still be seen but are not common. The use of tenofovir alafenamide (TAF) instead of tenofovir disoproxil fumarate (TDF) has reduced the incidence of tenofovir nephrotoxicity.

Diabetic nephropathy is unrelated to HIV.

22. **Answer:** D

SGLT2i can cause an acute transient dip in GFR of up to 20% to 30%, thought to be due to SGLT2i-induced afferent arteriolar vasoconstriction. It is suggested that the natriuretic effect of SGLT2i leads to tubuloglomerular feedback and afferent arteriolar vasoconstriction even in denervated kidney allograft. Once initiated, SGLT2i can be continued until dialysis initiation or transplantation (KDIGO 2024) unless it is no longer tolerated by patients. SGLT2i have been shown to reduce the rate of kidney disease progression in patients with CKD, irrespective of diabetes status, primary kidney disease, or kidney function.

23. **Answer:** C

Cisplatin-induced kidney injury may present clinically as acute tubulointerstitial nephritis, tubular necrosis, proximal S_3 tubular damage with salt wasting (K^+, Mg^{2+}, Ca^{2+}), Fanconi syndrome, and even nephrogenic DI. Given significant natriuresis and hypophosphatemia, mild tubular proteinuria, and glucosuria in the absence of hyperglycemia, the patient likely has cisplatin-induced Fanconi syndrome and renal salt wasting.

There is no sign of AIN (absence of rise in SCr or WBCs in the urine).

Malignant pericardial effusion and adrenal insufficiency may present with hyaline casts in the urine but typically without proteinuria or glucosuria.

24. **Answer:** B

Combined creatinine and cystatin-based equation to estimate GFR has been demonstrated to be the most accurate. CG formula overestimates creatinine clearance in patients with excessive

weight due to adipose tissue or volume (weight is in the numerator). (Stevens, Paul E. et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*; 105(4):S117 - S314.)

25. **Answer:** C

    This patient presents with classic symptoms of Fabry disease, the second most prevalent lysosomal storage disease (after Gaucher disease) that may be seen in all ethnicities and races. Fabry disease is caused by an X-linked inborn error of metabolism with deficiency or defect of lysosomal hydrolase α-galactosidase A (α-Gal A), an enzyme that catalyzes the hydrolytic cleavage of the terminal galactose from Gb3, thus leading to lysosomal accumulation of Gb3 in various cells including vascular endothelium and smooth muscle cells, cardiac muscle cells and conduction fibers, kidneys, and nerve root ganglia.

    Clinical manifestations include:

    Neurologic: neuropathic pain in extremities, stroke at an early age

    Dermatologic: telangiectasias; angiokeratomas in groin, hip, periumbilical areas; corneal opacities; thickened lips; bullous nose; and hypohidrosis with associated heat/exercise or cold intolerance

    Cardiac: arrhythmias, left ventricular hypertrophy, HF, and valvular abnormalities

    Gastrointestinal (GI): abdominal pain, nausea, vomiting, diarrhea, or constipation. Often initially misdiagnosed as irritable bowel syndrome

    Renal: proteinuria (both tubular and glomerular proteinuria possible), progressive CKD, Fanconi syndrome due to proximal tubular injury, polydipsia and polyuria due to distal tubular injury and associated defective urinary-concentrating ability, multiple renal sinus and peripelvic cysts on imaging studies

    Make sure to review Fabry disease including diagnosis and treatment.

26. **Answer:** B

eGFR based on cystatin c may be appropriate if no comorbid illness other than reduction in muscle mass.
Malnutrition and advanced cancer are associated with an inflammatory state, which may affect cystatin c levels.
The effect of anabolic steroid on cystatin c is not known.
For all conditions listed above other than anorexia, measured GFR is suggested if it would impact treatment decisions (Stevens, Paul E. et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*; 105(4):S117 - S314). "Practice point 1.2.2.2: Where more accurate ascertainment of GFR will impact treatment decisions, measure GFR using plasma or urinary clearance of an exogenous filtration marker."

27. **Answer:** A
In patients with or without CKD, the best agent to use for volume overload is a loop diuretic.
Although SGLT2i induces a mild diuretic effect, its use is not indicated for the sole purpose of diuresis. However, the addition of SGLT2i in patients receiving a loop diuretic should prompt consideration for dose reduction of the loop diuretic.
Thiazide diuretic is too weak to use in managing hypervolemic state.
Review indications for using an SGLT2i in patients with CKD.
SGLT2i is recommended for use in individuals with CKD with eGFR greater than 20 mL/min/1.73 m^2 and:
    - T2D, or
    - Urine ACR 200 mg/g or more, or
    - HF, irrespective of the level of albuminuria

SGLT2i is suggested for use in individuals with eGFR 20 to 45 mL/min/1.73 m^2 with urine ACR 200 mg/g or less.

28. **Answer:** B
MEST-C classification predicts renal outcome: M1, S1, ≥T1, and ≥C1 are associated with worse prognosis; M1, S1, and T1/T2 are

additive. Note that MEST-C is not used to guide treatment or predict treatment response.
IgA vasculitis outcome is associated with E1.
Presenting factors that portend worse prognosis for IgAN: proteinuria greater than 1 g/d, HTN (DBP ≥95 mm Hg or antihypertensive therapy), persistent hematuria, SCr ≥1.5 mg/dL, histologic findings with greater MEST-C scores. Calculator for disease progression based on the IgAN International Prediction Tool:
https://qxmd.com/calculate/calculator_839/international-igan-prediction-tool-post-biopsy-adults
The calculator predicts the risk of 50% decline in eGFR or ESKD after a landmark time based on clinical and histologic variables at the time of kidney biopsy, including eGFR, BP, proteinuria, age, race/ethnicity (White, Japanese, Chinese, or other), prior use of ACEi/ARB, Oxford MEST-C histology scores, and immunosuppression use at or prior to biopsy.
This risk stratification tool does not predict responses to any particular treatment.

29. **Answer:** B
Current patient's eGFR decline is (67 − 52) ÷ 67 = 22%. This percentage of eGFR decline cannot be assumed to be expected but should be evaluated for any reversible cause.
Review KDIGO 2024 recommendations below:
GFR and albuminuria changes that warrant evaluation include:
- A reduction in eGFR more than 20% on a follow-up test warrants evaluation.
- A reduction in eGFR more than 30% following hemodynamically active therapies (eg, addition of ACEi, ARB, or SGLT2) warrants evaluation. A reduction of less than 20% to 30% may be expected and is generally transient. This lower level of eGFR reduction is thought to provide long-term cardiac and kidney protective effects. Reflexive discontinuation of these cardioprotective and kidney protective agents should be

avoided. However, close monitoring to ensure no further reduction in eGFR is warranted.

- Doubling of ACR at a subsequent visit warrants evaluation.

30. **Answer:** A
    Modification of immunosuppressive therapy (IST) (ie, intensifying or reinitiating therapy) based on increasing ANCA titer alone is not recommended. ANCA titer increase alone does not necessarily indicate relapse. IST intensification without clinical evidence of active disease is not benign.
31. **Answer:** D
    Lower KDPI values are associated with longer estimated function, whereas higher KDPI values are associated with shorter estimated function (eg, a kidney with a KDPI of 20% is expected to have longer longevity than 80% of recovered kidneys). Kidney transplantation confers survival advantages over remaining on dialysis across all ages and in both transplant recipients with diabetes and nondiabetes. Given the patient's age and the prolonged waiting time for a deceased donor kidney, excluding deceased donor kidneys with KDPI more than 85% may decrease his chance of ever receiving a kidney transplant, hence lower survival. The 10 donor characteristics used to calculate the KDPI include donor age, height, weight, ethnicity, history of HTN, history of diabetes, SCr, cause of death, hepatitis C, and donation after circulatory death status. Gender is not one of the factors used in calculating KDPI.
32. **Answer:** C
    A reversible decrease in GFR may occur following the initiation of SGLT2i. In general, it is acceptable if the fall in eGFR is less than 30% from baseline. However, a "GFR reduction of >30% on subsequent testing exceed the expected variability and warrant evaluation" (Stevens, PA et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2017;105(4):S117-S314). Current patient's eGFR decline is (45 − 30) ÷ 45 = 33.3%. Dapagliflozin should be held, and an evaluation for any other cause of eGFR decline

should be performed. If nothing can be found, consider using a lower dose of dapagliflozin with close monitoring of kidney function.

33. **Answer:** B

This patient has an increased SAG and low serum bicarbonate, concerning for a high SAG metabolic acidosis. RTA is unlikely, given the high SAG. Obtaining urine studies is not needed.

The patient denies any history of difficulty with voiding. Obstruction is a less likely diagnosis.

Obtaining liver function tests and lipase is reasonable, but the examination is nonspecific. There is no localized abdominal pain.

The presenting case is concerning for euglycemic ketoacidosis. This condition is thought to be due to an imbalance in insulin and glucagon ratio. SGLT2i glucose-lowering effect reduces insulin secretion, thereby allowing unopposed glucagon to induce lipolysis and ketoacidosis. Greater than 70% of reported cases occurred with serum glucose less than 250 mg/dL. For this reason, SGLT2i-associated ketoacidosis is also referred to as "euglycemic ketoacidosis."

Risks include type 1 DM (but can occur in T2D), female, excessive reduction or discontinuation of insulin, major surgery or trauma, reduced oral intake, alcohol consumption, concurrent use of metformin, and low carbohydrate intake (eg, ketogenic diets).

Patients may present with nonspecific symptoms such as abdominal pain, nausea/vomiting, and/or fatigue and evidence of an increased SAG. Volume depletion is typically mild or absent due to the lack of severe hyperglycemia and associated osmotic diuresis.

Strategies to reduce risks for SGLT2i-associated ketoacidosis

- The use of SGLT2i in patients with type 1 DM is contraindicated (FDA warning).
- Discontinue SGLT2i in acute illnesses, particularly in association with poor oral intake.
- Discontinue SGLT2i 48 to 72 hours prior to major surgery.

- Avoid insulin dose reduction of greater than 20%.
- Avoid ketogenic diets and alcohol ingestion.
- Permanently discontinue SGLT2i in patients with SGLT2i-associated ketoacidosis.
- Treatment is similar to diabetic ketoacidosis (DKA). However, patients with SGLT2i-associated ketoacidosis may need early glucose infusion (ie, 5% or 10% dextrose drip) to prevent hypoglycemia while concurrently allowing for sufficient endogenous insulin secretion to suppress ketone formation and close the SAG.

34. **Answer:** C

Males can have higher urinary creatinine excretion, thus falsely low ACR (the urine ACR decreases if creatinine increases).

High protein intake can also have higher urinary creatinine excretion, thus falsely low ACR.

Loop diuretic increases urine flow and can change the concentrations of both albumin and creatinine, thus no change in ACR.

Hematuria (eg, menstruation) or infection can increase ACR or urine protein to creatinine ratio.

Of note, exercise can increase albumin and protein in the urine, but it can also increase urinary creatinine excretion. ACR measurements during exercise may not be accurate.

35. **Answer:** C

Hydroxychloroquine maintenance therapy should be continued during pregnancy. Discontinuation of hydroxychloroquine may lead to lupus flares, including LN.

Start low-dose aspirin 100 mg/d or less at conception or as soon as pregnancy is recognized to reduce the risk of preeclampsia, intrauterine growth retardation, and fetal loss.

LN relapse during pregnancy should be treated with GC, and if necessary, AZA.

The use of MPA during pregnancy is contraindicated due to concerns for teratogenicity. Patient on maintenance MPA should

be switched to AZA during and for the duration of pregnancy. AZA should be switched back to MPA following delivery. Data on breastfeeding safety are lacking.

36. **Answer:** D

The family history is notable for the same condition on his paternal side only, suggesting a high possibility of an autosomal dominant condition.

ADTKD is previously known as medullary cystic kidney disease. ADTKD is a rare kidney disease characterized by tubular damage and interstitial fibrosis with normal glomeruli that progresses to ESKD in adulthood. Subclassification of ADTKD is based on specific gene mutations involving UMOD, MUC1, REN, HNF1β, or SEC61A1. Histopathology reveals nonspecific interstitial fibrosis and tubular atrophy out of proportion to chronic vascular or glomerular disease, with or without tubular cysts, and with minor inflammation.

ADTKD-UMOD subtype is the most common subtype of ADTKD that involves mutation of UMOD, encoding uromodulin, also known as Tamm-Horsfall glycoprotein. Mutated uromodulin proteins are trapped in tubular epithelial cells, which leads to tubular cell apoptosis, reactive interstitial fibrosis, and cyst formation. ADTKD-UMOD is associated with a defective function of the thick ascending limb of Henle loop, salt wasting, volume depletion, hyperuricemia, gout, and ESKD early in the third to seventh decades of life.

ADTKD-HNF1β subtype involves mutation of HNF1β, encoding the HNF1β, a transcription factor involved in the early development of neural tube, lung, kidney, and GI and genital tracts. ADTKD-HNF1β is associated with maturity-onset DM of the young type 5, renal cyst, hypomagnesemia, hypokalemia, and hypocalciuria. The latter is via reduction in calcium-sensing receptor and claudin 19 and 10b.

Autosomal recessive tubulointerstitial disease is characterized by urinary-concentrating defects, chronic tubulointerstitial nephritis, cyst formation, and progression to ESKD, typically by the age of

30. NPHP is classified based on age of onset as infantile, juvenile, or adolescent. NPHP is one of the most common genetic disorders leading to ESKD in children.
Clinical manifestations

- Age of onset: in utero but age of symptom onset depends on specific mutated *NPHP* gene
- Polyuria, polydipsia requiring fluid intake at night, secondary enuresis, anemia, growth retardation, may be hyperuricemia
- Extrarenal manifestations reflecting a ciliopathy syndrome occur in 10% to 20% of cases and include retinal defects (retinitis pigmentosa, ocular apraxia, nystagmus, coloboma), liver fibrosis, cardiac malformation, situs inversus, bronchiectasis, ulcerative colitis, skeletal abnormalities (polydactyly), and neurologic abnormalities (encephalocele, vermis aplasia, hypopituitarism).
- ESKD by the third decade of life but may range from the first few years to the fifth decade of life depending on the affected gene.

Tuberous sclerosis syndrome is not associated with hyperuricemia/gout, renal salt wasting, or having small shrunken kidneys.

37. **Answer:** D
KDIGO 2012 suggests alkalinization of patients with CKD to keep serum bicarbonate (total CO_2) in the range of 22 to 29 mmol/L.
Review adverse clinical effects associated with metabolic acidosis

- Increased protein degradation, catabolic rate, muscle wasting
- Impaired vitamin D synthesis, bone metabolism, loss of bone density
- Altered endocrine functions: decreased insulin sensitivity, decreased insulin-like growth factor 1 (IGF-1) levels and responsiveness of IGF-1 to growth hormone administration, and reduced thyroid function (reduced T3 and T4 with normal thyroid-stimulating hormone and blunted response to thyrotropin)

- Accelerated CKD progression (due to activation of profibrotic and pro-inflammatory pathways and worsening of proteinuria and tubulointerstitial injury mediated by Ang II, endothelin 1, aldosterone, and intrarenal ammonia)
- Increased all-cause mortality in CKD, ESKD, and renal transplant recipients
- Others: increased oxidation of branched-chain amino acids (valine, leucine, isoleucine); decreased albumin synthesis

(Kidney Disease Improving Global Outcomes. KDIGO metabolic acidosis infographic set 2022. Accessed April 25, 2024. https://kdigo.org/wp-content/uploads/2022/08/KDIGO-Metabolic-Acidosis-Infographic-Set-2022.pdf)

38. **Answer:** B

This patient presents with AKI along with an active urinary sediment and significant albuminuria, suggestive of a GN. A kidney biopsy is warranted. The patient has no evidence of cirrhosis on examination. Hyperoncotic albumin has no benefit in this patient with acute GN. Although it is reasonable to obtain liver function tests in a patient with a history of alcohol use over the weekends, it is likely not helpful in the diagnosis of the current patient's underlying AKI. Dysmorphic RBCs are consistent with a glomerular, not collecting system source. A urology consult is likely not yet necessary at this time.

39. **Answer:** D

The use of tolvaptan should be avoided in patients with liver disease because of their potential to cause serious and fatal liver injury.

Salt tablets can worsen this patient's fluid accumulation associated with cirrhosis.

Lithium may induce nephrogenic DI, which could alleviate this patient's hyponatremia. However, lithium may cause kidney injury and worsen this patient's kidney function (eg, chronic tubulointerstitial nephritis, FSGS).

Increasing solute intake load (eg, increasing solid food, proteins) may improve water excretion. This is the safest treatment option

for the current patient.

40. **Answer:** B

STS used in the treatment of calcific uremic arteriolopathy (calciphylaxis) has been reported to be associated with elevated SAG metabolic acidosis. The underlying mechanisms may include interference with mitochondrial oxidative phosphorylation, causing lactic acidosis and the formation of thiosulfuric acid and hydrogen sulfide. Management is discontinuation of STS and supportive care.

Vancomycin toxicity may cause kidney injury, hearing loss, "red man" syndrome, and other less common side effects such as neutropenia, eosinophilia, or vasculitis/phlebitis, but no altered mental status.

The patient's K_t/V is 1.4. Dialysis is adequate.

The patient has no signs of sepsis—negative blood cultures, no fevers.

41. **Answer:** D

Although most azole antifungals are metabolized by the liver and do not require dose reduction, fluconazole is significantly excreted in the urine and requires a 50% dose reduction for GFR below 60 mL/min. Fluconazole is dialyzable, and the dose should be given after dialysis. Voriconazole, ketoconazole, itraconazole, and posaconazole are not dialyzable. It is the accumulation of cyclodextrin mixed in the IV formulations of itraconazole, voriconazole, and posaconazole that leads to altered mental status, not the azoles themselves. Most azoles are potent inhibitors of CYP34A and can significantly increase drug levels of CNIs. Voriconazole, ketoconazole, itraconazole, and posaconazole are strong inhibitors of CYP3A4. Fluconazole and isavuconazole are moderate CYP3A4 inhibitors. In general, echinocandins (micafungin, anidulafungin) do not alter CNI levels. Caspofungin, however, has been reported to reduce tacrolimus levels.

42. **Answer:** D

Primary hyperparathyroidism (hPTH) should present with hypercalciuria, not hypocalciuria. The patient does not need a

parathyroidectomy.

This patient's laboratory studies are not consistent with having high FGF-23 levels. FGF-23 is inhibitory to the production of $1,25(OH)_2$ vitamin D. The current patient's $1,25(OH)_2$ vitamin D level is high, not low.

The anti–FGF-23 antibody burosumab was FDA approved in 2018 for the treatment of X-linked hypophosphatemia (XLH) in patients older than 6 months of age and hypophosphatemia associated with tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients aged 2 years or above.

The 24-hour urine collection is adequate (body weight × 15-20 mg/kg) = 70 × 15 to 70 × 20 mg = 1,050 to 1,400 mg/d. A high urine volume does not imply an overcollection.

The current patient likely has familial hypocalciuric hypercalcemia (FHH), given her very low urine calcium despite having hypercalcemia. Some patients with FHH may respond to calcimimetics. It is reasonable to consider a trial of calcimimetic in addition to supportive care therapy.

43. **Answer:** D

Criteria for the diagnosis of HRS based on the Ascites International Club

- Diagnosis of cirrhosis with ascites
- AKI as defined per AKIN/KDOQI:
  - Increase in SCr by 0.3 mg/dL or more from stable baseline in less than 48 hours, OR
  - 50% or higher increase from baseline, which is known, or presumed, to have occurred within the prior 7 days

1. No improvement in SCr after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended albumin dose: 1 g/kg of body weight per day up to a maximum of 100 g/d)
2. Absence of shock

3. No current or recent treatment with nephrotoxic drugs (eg, no recent use of antibiotic or NSAIDs)
4. Absence of macroscopic kidney injury, that is, proteinuria less than 500 mg/d, microhematuria less than 50 RBCs/HPF, and normal renal ultrasonography

44. **Answer:** C

Ritonavir is a potent CYP3A4 inhibitor. The use of Paxlovid and CNIs combination therapy can result in markedly elevated CNI levels and nephrotoxicity. CSA is both a substrate and an inhibitor of the CYP3A4 enzyme system. Concomitant use of drugs that are extensively metabolized by the CYP3A4 enzyme system (*such as statins*) can result in a significant increase in *statin* drug level and, therefore, risk for statin-induced rhabdomyolysis. Tacrolimus is a substrate but not an inhibitor of the CYP3A4 enzyme system; therefore, tacrolimus does not affect *statin* drug level. Allopurinol interferes with the metabolism of AZA, which leads to a significant increase in 6-mercaptopurine levels and resultant severe bone marrow suppression (pancytopenia).

45. **Answer:** B

"Full-house" immunofluorescence staining for IgG (strong), IgA, IgM, C1q (strong), and C3 is classic for LN. On electron microscopy, deposits may be seen at locations other than subepithelial regions (eg, mesangial, subendothelial, and intramembranous) in class V LN. In primary MN, deposits are predominantly seen in subepithelial regions only. Endothelial cell tubuloreticular inclusions are usually present in LN. Note that endothelial cell tubuloreticular inclusions may also be seen in glomerular diseases associated with viral infections or interferon therapy.

46. **Answer:** B

Individuals with a history of alcoholism, typically with a recent history of binge drinking and concurrent poor oral intake, persistent vomiting, and/or volume depletion, are at risk for AKA. Clinically, patients can present with a sweet ketone breath, and elevated SAG metabolic acidosis that can be severe with blood pH

less than 7 with or without concurrent metabolic alkalosis from volume depletion and vomiting. Unlike DKA where ketone bodies include acetone, acetoacetic acid, and β-hydroxybutyrate, the predominant ketone body in AKA is β-hydroxybutyrate. The ratio of β-hydroxybutyrate to acetoacetic acid prior to treatment is typically at a 5:1 ratio in patients with AKA. Treatment is the administration of glucose plus normal saline. The former is to stimulate insulin secretion. AKA is characterized by severe metabolic acidosis that is rapidly corrected with glucose plus normal saline infusion. Thiamine should also be administered to reduce the risk of precipitating Wernicke encephalopathy or Korsakoff syndrome associated with glucose administration. HD may be considered in severe metabolic acidosis with poor response to conservative supportive therapy.

DKA is typically associated with higher glucose levels (but not necessarily, particularly in the case of euglycemic ketoacidosis associated with the use of SGLT2i) and lower β-hydroxybutyrate to acetoacetic acid ratios.

Starvation ketosis usually presents with mildly elevated SAG because ketoanion levels are typically only 3 to 5 mmol/L. The ketone bodies initially produced in SKA can, in turn, stimulate pancreatic islets to release sufficient insulin to hinder further lipolysis, rendering SKA a self-limiting process.

PA is associated with chronic use of acetaminophen in malnourished, older, chronically ill, and/or debilitated individuals. In the case of PA accumulation alone, lactic acid and ketone levels should be absent.

47. **Answer:** D

This patient has metabolic acidosis, kidney failure with a low SAG, and proteinuria mismatch. The reason for the kidney failure is likely cast nephropathy. Evaluation for paraproteinemia is indicated.

RTA is typically not diagnosed in patients who present with kidney failure as renal tubular dysfunction is part of the kidney failure. In addition, patients with underlying RTA who present with kidney

failure tend to have acidemia out of proportion to the degree of kidney failure.

There is no laboratory evidence of obstructive uropathy (no hyperkalemia with severe metabolic acidosis) and no classic clinical evidence of retroperitoneal fibrosis (eg, nonspecific abdominal/back pain, unexplained leg deep venous thrombosis [DVT]).

Patients who develop metabolic acidosis from chronic acetaminophen use due to 5-oxoproline (5-OXO) (pyroglutamate) accumulation present with a high SAG metabolic acidosis. Chronic acetaminophen use in malnourished or chronically ill patients may be associated with elevated SAG metabolic acidosis due to the excess production of 5-OXO (aka PA) by γ-glutamylcysteine synthetase from the γ-glutamyl cycle. This is due to the lack of negative feedback of γ-glutamylcysteine synthetase activity by glutathione. In physiologically stressed or malnourished patients with increased oxidative stress, glutathione levels are reduced. The additional use of acetaminophen further depletes glutathione because glutathione is used in the metabolism of acetaminophen. Also note that pyroglutamate accumulation is a chronic process. Acetaminophen levels may not be increased.

48. **Answer:** A

Hypokalemia is the most important electrolyte disturbance associated with metabolic alkalosis. It is important clinically to replace potassium in patients with metabolic alkalosis because hypokalemia can cause persistent metabolic alkalosis.

Severe hypokalemia can contribute to persistent metabolic alkalosis due to several mechanisms.

Hypokalemia can increase ammoniagenesis, hence facilitated H^+ secretion; increase H^+ secretion via increasing sodium-hydrogen exchanger (NHE3) and sodium bicarbonate exchanger activities in proximal tubules; reduce NKCC2 activity, thereby increasing sodium delivery to epithelial sodium channel (ENaC), generation of negatively charged lumen, and resultant facilitated H^+ secretion; increase H^+-K^+-ATPase activity in collecting duct;

reduced pendrin expression and activity in β-intercalated cell (β-IC) in collecting duct.

Hypomagnesemia (not hypermagnesemia) may present with metabolic alkalosis via associated hypokalemia.

Hypercalcemia (not hypocalcemia) blocks the renal outer medullary potassium channel, which indirectly blocks the sodium potassium 2 chloride cotransporter to cause metabolic alkalosis.

49. **Answer:** D

Both live and live-attenuated vaccines are contraindicated in the post-transplantation period. Mumps, measles, and rubella (MMR) vaccine uses live-attenuated virus. Vaccinations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients. Vaccinations during the first 3 months after transplantation may result in suboptimal response and protection because of heavy immunosuppression. Most centers restart vaccinations 6 to 12 months after transplantation, and 3 months post-transplantation for influenza during outbreaks. Vaccinations should be administered 4 weeks or more before transplant to achieve optimal response and, in the case of live or live-attenuated vaccines, to minimize the possibility of live vaccine–derived infection in the post-transplantation period.

50. **Answer:** B

The only diagnosis that is consistent with metabolic alkalsosis with high urine chloride above is milk-alkali syndrome. Both acute and chronic vomiting are associated with hypovolemia and low urine chloride. Milk-alkali syndrome refers to chronic ingestion of milk and calcium carbonate (alkali). Metabolic alkalosis is caused by the exogenous alkali, not by bicarbonate retention due to inadequate luminal chloride seen in hypovolemic states. Serum calcium levels may also be high in these patients.

Posthypercapnia is associated with chloride-sensitive metabolic alkalosis. Chronic hypercapnia (chronic CO_2 retention) leads to compensatory renal HCO_3^- retention in exchange for Cl^- to maintain optimal acid-base status. The acute correction of hypercapnia (eg, with acute mechanical ventilation) leaves behind

the residual compensatory high serum HCO_3^- and low Cl^- state, which is seen as chloride-sensitive metabolic alkalosis.

51. **Answer:** C
Each parental chromosome 6 provides a linked set of major histocompatibility complex (*MHC*) genes (called a haplotype) to the offspring in a Mendelian codominance inheritance. In two unrelated individuals, it is not possible to identify haplotypes from the phenotypic information alone because it is not known which antigen belongs to which one chromosome to determine linkage. However, if the donor and recipient were siblings, then it is possible to identify a shared haplotype of the family as A1, B8, DR4, and DQ2 and an unshared haplotype A25, B50, DR11, and DQ6.

52. **Answer:** D
Infusion of hyperoncotic albumin in patients intravascularly volume-depleted cirrhosis who have no peripheral edema only increases intracapillary oncotic pressure, but not hydraulic pressure (lack of interstitial edema fluid shift into capillaries). This change in intracapillary hemodynamics can decrease net peritubular capillary perfusion pressure and precipitate acute tubular necrosis (ATN). Infusion of hyperoncotic albumin may be beneficial for any of the other three patients.

53. **Answer:** B
She has ketoacidosis secondary to dextrose-free CKRT solution and malnutrition. Both malnutrition and loss of glucose into a glucose-free dialysate with CKRT promotes gluconeogenesis and ketogenesis. Additionally, inadequate insulin administration in patients with DM may also contribute to ketoacidosis.
Insulin resistance in the setting of critical illness may also play a role in ketoacidosis.
Incorrect answers: Although patient had a large bowel resection, gut bacterial overgrowth to result in D-lactic acidosis is unlikely to occur so quickly after bowel resection.
Pyroglutamate acidosis may be seen with high-dose acetaminophen use in the ICU. However, in this case, there is no

history of acetaminophen use.
Her serum creatinine and potassium levels improve significantly with CKRT so choice D is not correct.

54. **Answer:** D
Paraprotein fragments may activate complements and present as C3G.
Postinfectious GN is mediated by complements.
Mutations/genetic variants of complement regulators can cause dysregulation of the alternative complement pathway and cause C3G.

55. **Answer:** B
Electron microscopy shows enlarged atypical proximal tubular mitochondria with broken cristae associated with nucleotide reverse transcriptase inhibitor (tenofovir) treatment (×10,000). The use of tenofovir may also be associated with Fanconi syndrome, salt wasting, and acute tubular injury.

56. **Answer:** D
Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of purine metabolism that leads to kidney stones and CKD. APRT deficiency prevents adenine recycling (from the purine nucleotide salvage pathway) and leads to adenine accumulation. Xanthine oxidase metabolizes the accumulated adenine to 2,8-DHA, which is insoluble in the urine and can cause kidney injury with or without stone formation. 2,8-DHA stone is radiolucent and may be mistaken as uric acid stone. Low-dose allopurinol or febuxostat with uptitration as needed for the disappearance of 2,8-DHA crystals in the urine sediment has been suggested. Optimal dosing has not been defined.

57. **Answer:** C
Kidney donor profile index (KDPI) provides an estimate of the likelihood of graft failure after a deceased donor kidney transplant. It does not provide information on rejection risk. Lower KDPI values are associated with longer estimated function, whereas higher KDPI values are associated with shorter estimated

function (eg, a kidney with KDPI of 20% is expected to have longer longevity than 80% of recovered kidneys).

58. **Answer:** B

There is no benefit in using sodium bicarbonate over normal saline in hydrating patients for renoprotection against radiocontrast-associated kidney injury. Because of this, if sodium bicarbonate is selected over normal saline by the clinician for any reason, the clinician should make sure no harm is done. In this case, the patient has hypocalcemia. Alkalinizing the blood may reduce ionized calcium levels, which could cause harm to the patient. Normal saline should, therefore, be the solution of choice. The use of *N*-acetylcysteine has not been shown to provide any added benefit. Data regarding remote ischemic preconditioning are conflicting.

59. **Answer:** B

The patient most likely has a urine leak. Urine leak commonly occurs within the first few days or weeks after transplant. The patient may present with pain over the allograft or abdominal pain (which is often severe). Creatinine concentration from JP drain fluid (or fluid drained from the incision) of at least 1.5 to 2 mg/dL greater than that measured for serum is suggestive of a urine leak. Surgical wound drainage creatinine values are often greater than 20 mg/dL in high-volume urine leaks. This patient's creatinine concentration from JP fluid drain was significantly higher than serum creatinine (50 vs 3.5 mg/dL).

Although the patient was highly sensitized at the time of transplant and tacrolimus level was subtherapeutic, acute rejection generally manifests as asymptomatic acute rise in SCr. In the era of potent immunosuppression, oliguria and allograft pain are usually absent unless immunosuppression is completely discontinued. In addition, JP drain fluid creatinine is similar to SCr in acute rejection.

Although a large lymphocele can compress the adjacent kidney allograft causing obstructive uropathy, lymphocele fluid creatinine is similar to SCr.

60. **Answer:** B

Having crescents alone without rapidly progressive declining in kidney function does not define RPGN. Of note, fibrocellular crescents signify subacute, not active "freshly" evolving crescents.

"The definition of glomerular crescent as given by the WHO is, two or more layers of cells partially or completely filling the glomerular space. Diffuse crescents when present usually imply a poorer prognosis, however, focal crescents may be reversed if the disease is detected early and could be adequately treated. The presence of diffuse crescents in >50% of the nonsclerosed glomeruli in the renal biopsy is termed as crescentic glomerulonephritis" (Chauhan S, Jain S, Garg N, Dixit S, Sharma S. Crescents in kidney biopsy—what do they imply? A clinicopathologic study of 40 cases in a tertiary care center. *J Microsc Ultrastruct*. 2021;9[2]:81-85).

Mesangial expansion and hypercellularity on light microscopy are classic findings of IgAN. "IgA" deposits need to be confirmed on immunofluorescence microscopy because the same pattern found on light microscopy may be seen in C1q nephropathy or IgM nephropathy.

61. **Answer:** D

In people with CKD G3 -G5, we (KDIGO 2024) recommend using an externally validated risk equation to estimate the absolute risk of kidney failure (1A).(*Kidney Int*. 2024;105[suppl 4S]:S117-S314.)

KDOQI 2015: The decision to initiate maintenance dialysis should be based primarily on signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to medically manage metabolic abnormalities and/or volume overload safely rather than on a specific level of kidney function.

62. **Answer:** D

It is true that current high BP may reflect ongoing pain after fall. If patient had pain-related HTN, then there is no need to intensify her current antihypertensive regimen at this time. However, given the history of frequent falls and normal neurologic examination,

the question of pseudohypertension should be raised. Patient may have been treated with antihypertensive agents inappropriately, which may have led to hypotensive episodes and associated multiple falls. Pseudohypertension is defined as having cuff DBP greater than 10 to 15 mm Hg higher when compared with intra-arterial pressure because of excessive atheromatosis and/or medial hypertrophy in arterial tree. This condition may be diagnosed by the Osler maneuver. Osler maneuver is positive when either brachial or radial artery remains palpable despite loss of pulse by auscultation following inflation of BP cuff.

If this patient had true HTN, the addition of a diuretic may be reasonable. However, it must be noted that trace to 1+ bilateral ankle does not necessarily require the use of diuretics. The cause for the edema must be first investigated. Given her current use of amlodipine, CCB-associated edema must be considered, in which case, the use of diuretic is not needed. Adding an MRA may be considered in patients with difficult-to-treat HTN. However, true HTN must be first established in this patient.

63. **Answer:** A

The patient has stigmata of liver disease including relative macrocytic anemia, upper limit liver size, and elevated AST and evidence of poor oral intake with low serum albumin and BUN. She is likely a "closet alcohol drinker." All other conditions likely present with a more concentrated urine (ie, higher urine specific gravity/osmolality). Primary adrenal insufficiency typically presents with hyperkalemia. There is no evidence of hypothyroidism on examination (normal reflexes, lack of hypothermia). The low urine specific gravity is consistent with a dilute urine, hence low osmolality, which would rule out SIADH.

64. **Answer:** D

AKI in association with a significant acute increase in proteinuria and hematuria in a patient with nephrotic syndrome, in particular MN, should raise concerns for acute renal vein thrombosis. This patient has an increased risk for thrombotic complications, given his severe hypoalbuminemia (serum albumin <<2.5 g/dL). Acute

worsening of proteinuria has been described in patients who present with renal vein thrombosis. Whether it is the worsening of NS that leads to renal vein thrombosis or the renal vein thrombosis that leads to the worsening of proteinuria is not clear. Although this patient will need a greater diuretic dose, the underlying reason for acute kidney injury needs to be evaluated immediately. Losartan-associated rise in SCr should not cause worsening of proteinuria.

65. **Answer:** A

Starfruit, rhubarb, and cranberry all contain high levels of oxalate. Chronic or excessive consumption of such fruits/vegetables can cause oxaluria, oxalate stones, and oxalate nephropathy. Ingestion of aristolochic acid–containing herbs can cause progressive chronic interstitial nephritis, proximal tubular injury, and increased uroepithelial malignancy risk.

66. **Answer:** B

First-line agents in the treatment of T2D include metformin and SGLT2i.

Metformin can be continued safely with very low risk of metabolic acidosis, with eGFR 30 mL/min/1.73 m^2 or more. It is suggested that metformin should not be initiated for eGFR 30 to 45 mL/min/1.73 m^2. B_{12} level should be monitored if metformin is used for greater than 4 years.

After metformin and SGLT2i, "patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred" (KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2022;102[suppl 5S]:S1-S127).

Long-acting GLP-1 RAs are prioritized ahead of insulin in individuals with T2D and CKD. Agents with proven renoprotection and cardiovascular benefit and without the need for dose adjustment in CKD include liraglutide, semaglutide (injectable), and dulaglutide.

Short-term use of a DPP-4i in combination with another oral agent does not appear to increase or decrease the risk of adverse atherosclerotic cardiovascular disease (ASCVD) outcomes. However, specific DPP-4i (saxagliptin or alogliptin) may increase the risk of hospitalization for HF. The U.S. FDA warns of the risk of hospitalization for HF with DPP-4i, specifically saxagliptin and alogliptin, and recommends discontinuation of these agents in patients who develop HF.

In addition, the use of GLP-1 RA and DPP-4i has no added benefit in terms of glycemic control and is not recommended by the FDA, American Diabetes Association, and American Clinical Endocrine Association.

Thiazolidinedione may confer ASCVD benefits but may increase the risk of edema. The current patient has a history of HFpEF and already presents with bilateral edema.

α-Glucosidase inhibitors have been suggested to confer ASCVD benefits, but their use must be cautioned in patients with CKD. See **Appendix 7.11**.

67. **Answer:** D

Shoulder pain (other than anginal causes) in a patient using PD may be caused by unintentional air infusion during dialysate solution instillation.

Management: Infuse full exchange volume, then drain dialysate with the patient in knee-chest position to remove the trapped air.

68. **Answer:** B

The first step should be to confirm medication adherence. Clues for nonadherence may be found in the lack of side effects associated with prescribed medications, for example, low pulse on high-dose β-blocker, tachycardia on potent vasodilators such as nifedipine, pedal edema with nondihydropyridine CCBs, some degree of hyponatremia, hypokalemia, and hypomagnesemia with thiazides. This patient appears to have none of the expected side effects from his antihypertensive regimen, albeit, not all patients will develop side effects. Regardless, pill count should be

considered to assess medication adherence prior to adding more medications.

69. **Answer:** D
Although choices A through C are all true statements, they are not consistent with the current patient's urine studies. There is a large urine protein and urine albumin difference (5.5 – 0.25 = 5.25 g/g). Tubular injury from stones or acute tubular injury does not cause proteinuria to this large degree. Typically, tubular proteinuria is below 2 g/g creatinine. Serum and urine protein electrophoresis and immunofixation and serum κ and λ must be obtained. Both paraproteinemia (eg, Bence Jones light chains) and SGLT2i can present with glucosuria. The former is due to generalized proximal tubular injury (Fanconi syndrome), and the latter is due to direct inhibition of glucose reabsorption via the SGLT2.

70. **Answer:** A
Characteristics suggesting cast nephropathy:
    - Urine free light chains (FLCs) 1,500 mg/L or more with concurrent low urinary albumin excretion
    - Fanconi syndrome: euglycemic glucosuria, phosphaturia, renal tubular acidosis
    - 24-hour urine protein electrophoresis and immunofixation with a predominance of monoclonal light chains
    - Proteinuria mismatch suggests the presence of free light chains (aka Bence Jones protein).
        - Urine dipsticks readily detect urine albumin, but not FLC, which is the protein that makes up the "cast" nephropathy. However, total urine protein measured as urine protein to creatinine ratio or 24-hour urine collection can detect and measure all forms of proteins, including FLC. Thus, in the presence of FLC, uPCR and 24-hour urine protein may be much greater than that measured on routine dipstick protein.

- Proteinuria mismatch may be unmasked by the addition of sulfosalicylic acid (SSA) to the urine sample because SSA precipitates all proteins including all albumin and FLC.

Characteristics suggesting glomerular process:
High-level albuminuria or nephrotic range proteinuria or syndrome suggests direct injury to the glomerular basement membrane: (monoclonal gammopathy–related) amyloidosis (most commonly AL amyloidosis), monoclonal Ig deposition disease, immunotactoid glomerulopathy, monoclonal cryoglobulinemic glomerulonephritis (IgM), proliferative GN with monoclonal Ig deposits, or C3G.
Acute tubular necrosis/injury generally does not present with proteinuria greater than 1 to 2 g/d. The current patient has greater than 8 g proteinuria/day.

71. **Answer:** A
The infusion of hyperoncotic albumin in a patient with markedly reduced kidney function and concurrent severe edema can lead to intravascular volume expansion, pulmonary edema, and acute respiratory decompensation. The patient is already very volume overloaded and not responding to high-dose diuretics. She appears to be already decompensating with her respiratory status, given her severe ascites and the ongoing use of hyperoncotic albumin without effective diuresis.
Performing a large-volume paracentesis at this time can reduce intra-abdominal pressure, help the patient breathe more easily, and improve central venous return. The latter may also help ameliorate the high ADH state to some degree. Both the improved venous return and reduced ADH state may serve to enhance diuresis, thereby improving hyponatremia.
Although terlipressin may be tried for presumed HRS AKI, the risk of respiratory failure is increased in patients with volume overload. In addition, terlipressin is contraindicated in patients with decompensating respiratory status.
Adding 3% saline or increasing the dose of 25% albumin is not advisable in this patient with severe volume overload and oliguria

not responding to diuretics.

72. **Answer:** C

Review the different categories of HTN.

Drug-resistant HTN can be defined as either the BP is not at goal despite optimal doses (optimal dose, defined as >50% of maximal dose recommended for treatment of HTN) of three different appropriate (eg, first-line) antihypertensive drug classes, ideally one class being a diuretic, or alternatively, BP is at goal with optimal doses of four appropriate antihypertensive drug classes, ideally one class being a diuretic.

Patients with *apparent* (drug)-resistant HTN are those who meet the criteria for drug-resistant HTN but have NOT been ruled out for proper BP techniques, white coat hypertension, noncompliance, and improper BP medication regimens (eg, using several vasodilators in a patient with increased heart rate without a β-blocker, using multiple sympatholytic drugs without any vasodilator, or using multiple drugs with reflex salt retention but without a diuretic). Our current patient is on an inappropriate combination of multiple vasodilators without any diuretics. In addition, the patient appears to have associated reflex tachycardia without any β-blocker to counteract the effect.

Refractory HTN is when the BP is not controlled despite being on five or more appropriate drugs, including a diuretic.

The term *pseudoresistant HTN* is used for patients who initially meet the criteria for "drug-resistant HTN" but later proven to fail meeting the same criteria following proper BP measuring techniques, ambulatory BP measurements, and/or compliance with proper BP medication regimens.

Apparent resistant HTN may be seen in 15% of the population treated for HTN in the United States, but approximately 50% of these patients have pseudoresistant HTN. True resistant HTN is approximately 5% of treated hypertensives.

73. **Answer:** B

Metformin is not associated with hyponatremia. The patient was previously on quetiapine without any problem. Her serum sodium

was normal 1 month ago when she was already taking quetiapine. Fluid restriction in this patient is likely ineffective because her baseline urine output is already very low (<800 mL/d as documented). Chlorthalidone remains the most likely cause of her severe hyponatremia. In particular, patients at high risk for thiazide-associated hyponatremia tend to be older women who have low baseline food intake. Both older age and low solute intake limit optimal water excretion.

74. **Answer:** D

Belatacept use has been shown to improve kidney function and metabolic outcomes, including hypertension, diabetes, and hyperlipidemia through avoidance of CNIs.

Both calcineurin inhibitors and mTOR inhibitors are diabetogenic.

Tacrolimus has been shown to be more diabetogenic than cyclosporine (CSA)

Of note, sirolimus or everolimus use is associated with the worst lipid profile (particularly hypertriglyceridemia) compared to CSA and tacrolimus.

75. **Answer:** B

Once initiated, it is reasonable to continue SGLT2i even when eGFR falls below 20 mL/min/1.73 m^2 unless not tolerated or KRT is initiated.

It is reasonable to hold SGLT2i during prolonged fasting, surgery, or critical medical illness due to concerns for increased risk for (euglycemic) DKA.

Use with caution in individuals at risk for hypovolemia. Consider lowering dose of diuretics prior to SGLT2i initiation.

76. **Answer:** A

This patient has a low normal cortisol level. A corticotropin-stimulating test may be obtained to confirm hypocorticolism. Hypocorticolism may occur in association with primary adrenal insufficiency or centrally with hypothalamic or pituitary insufficiency. In women with a history of obstetrical complications and associated blood loss, the diagnosis of Sheehan syndrome with associated hypopituitarism must be entertained. In this

condition, patients can present with central hypocortisolism and central hypothyroidism, along with low levels of growth hormone, follicular-stimulating hormone, and luteinizing hormone. A brain magnetic resonance imaging (MRI) or CT showing an empty or partial empty sella is diagnostic. This patient's history of cold intolerance and low body temperature on physical examination is consistent with hypothyroidism, although central, *not* peripheral in the current case. A normal thyroid-stimulating hormone level may rule out peripheral hypothyroidism, but not central hypothyroidism. A concurrent low free T4 level is needed to rule in central hypothyroidism.

Although this patient appears to have hypocorticolism, it is unlikely due to primary adrenal insufficiency because her serum potassium is not elevated.

Plasma aldosterone measurement is not indicated. There is no evidence of renal salt wasting. Urine sodium concentration is relatively low.

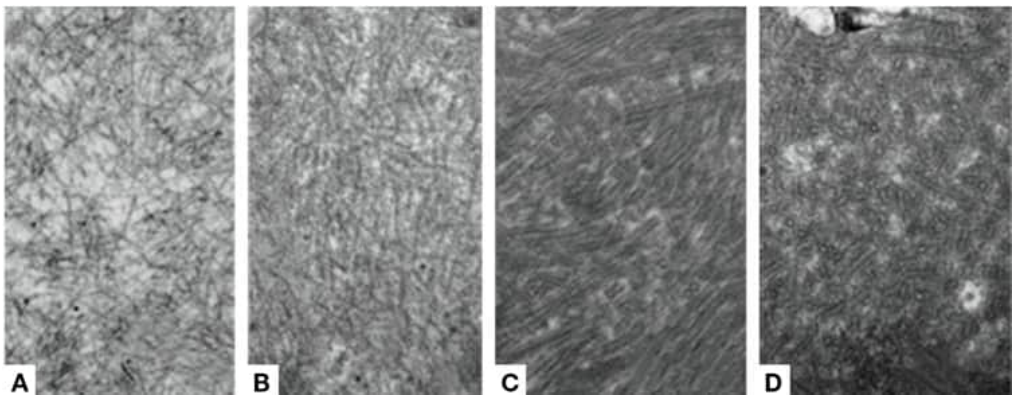
A copeptin level only serves as a surrogate for the ADH level. The high urine osmolality in this case already supports a high ADH state. Obtaining a copeptin level is not necessary.

77. **Answer:** A

The longer duration of action of chlorthalidone and indapamide compared with hydrochlorothiazide may confer better BP control, particularly nighttime BP control. There is no benefit in switching losartan to an ACEi. Of note, this is an Asian woman. It has been reported that Asian women may be more prone to getting ACEi-induced coughs. Although nifedipine is a more potent vasodilator compared with amlodipine, the patient reports a history of intolerance to nifedipine. It should not be given. Current 24-hour urine reveals a sodium of 90 mmol/d. This is equivalent to approximately 2 g of sodium. The patient is already adherent to dietary sodium restriction.

78. **Answer:** D

All statements are correct. Be familiar with the histopathology below.



Fibrillary deposits. A. Amyloid. Haphazardly arranged 10 nm fibrils. B. Fibrillary GN. Randomly arranged 15 to 25 nm fibrils. C. Immunotactoid GN. Parallel arrays of 35 to 50 nm microtubules, often monoclonal. D. Cryoglobulin. Randomly arranged to clusters of 20 to 30 nm curved microtubules (All × 72,000).

79. **Answer:** C

Alport syndrome (AS) due to mutations involving any α chain of type 4 collagen can be complicated by segmental glomerular scarring, taking the FSGS pattern of injury that can mimic primary or familial FSGS. Genetic analysis may help uncover other mutations associated with FSGS. In patients with AS-associated FSGS, the use of an ACEi or ARB (not GC) is recommended to slow down CKD progression.

80. **Answer:** B

This patient has stage 1 HTN (stage 1 is defined as having an average SBP between 130 and 139 mm Hg or DBP between 80 and 89 mm Hg) who already failed a 3-month trial of healthy lifestyle modification. Given the concurrent history of CKD, antihypertensive therapy initiation is now indicated. KIDGO 2024 suggests a goal SBP 120 mm Hg or less in individuals with CKD. Other indications for pharmacologic therapy in stage 1 HTN after a failed trial of healthy lifestyle modification include having concurrent T2D, known ASCVD, or 10-year ASCVD risk 15% or more.

The best antihypertensive agent for this individual is a renin-angiotensin inhibitor, given his CKD and albuminuria. In general, β-blocker is not a first-line antihypertensive agent unless there is a specific indication, for example, tachyarrhythmias.

81. **Answer:** A

Kidney failure risk calculator (kidneyfailurerisk.com): The kidney failure risk equations were developed in patients with CKD stages G3 to G5 referred to nephrologists in Canada and have been validated in greater than 1 million individuals and greater than 1 million events, spanning 30+ countries worldwide. The equations accurately predict the 2- and 5-year probability of treated kidney failure (dialysis or transplantation) for a potential patient with CKD stages 3 to 5. Calculated risk is based on the patient's age, sex, eGFR, ACR (four-variable equation) with or without calcium, phosphate, bicarbonate, and albumin (eight-variable equation).

Tangri calculator (ckdpcrisk.org/lowgfrevents/) has been shown to accurately predict 2- and 5-year kidney failure risks as well as nonfatal cardiovascular events and death risk for adults with eGFR less than 60 mL/min/173 m^2. Calculated risk is based on the patient's age, gender, race (Black or White), eGFR, SBP, history of cardiovascular disease, DM, urine ACR, and smoking history.

82. **Answer:** B

It is generally not necessary to switch PD to HD during pregnancy.

The ideal prescription for PD in pregnancy is not well established and remains to be defined. In general, it is advisable to perform low-volume/more frequent exchanges, particularly during the third trimester. The use of a cycler may be required to provide adequate therapy. Avoid 4.25% dextrose solution to avoid rapid fluid shift and hypotension.

Fetal outcomes for mothers requiring KRT: Preterm delivery may reach 80% among mothers receiving KRT. In general, conception prior to HD initiation is associated with higher live birth rates, but birth weight and gestational age are comparable to those conceived after HD initiation. The prevalence of small gestational age babies has been shown to be higher among mothers

receiving PD compared with those receiving HD. A tendency for greater birth weight with more intense HD has been reported.

Low-dose aspirin (75-150 mg/d) should be given to the pregnant woman with CKD prior to week 16 gestational age to reduce the risk of preeclampsia/eclampsia (PE/E).

83. **Answer:** D

Morphine and its active metabolites can accumulate in CKD and lead to central nervous system (CNS) toxicity (sedation, altered mental status, myoclonus, seizures) and respiratory depression. Its use in CKD is not recommended.

Both pregabalin and gabapentin are extensively renally cleared, and both are dialyzable. Dose adjustment is needed in CKD. Drug accumulation can lead to reduced consciousness, confusion, ataxia, myoclonus, tremulousness, and asterixis.

Tramadol is primarily hepatically metabolized. Approximately 30% of the dose is excreted in the urine as unchanged drug and 60% as metabolites. The accumulation of its active metabolite (*O*-desmethyltramadol) in CKD can lead to seizures and respiratory depression. The use of tramadol in advanced CKD is not recommended.

Fentanyl is rapidly metabolized in the liver. There does not appear to be any clinically significant accumulation of fentanyl in patients with advanced CKD.

84. **Answer:** D

Prior history of PTLD is not a contraindication to repeat transplant. However, patients should be disease free for at least 2 years prior to reallograft transplant (KDIGO guidelines: at least 2 years for nodal disease, and at least 5 years for extranodal and cerebral disease).

The use of acyclovir and ganciclovir is of unproven benefit because their activity is dependent on intracellular phosphorylation by virally coded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase.

Rituximab is a chimeric monoclonal antibody targeting CD20 on the surface of B cells. It is currently considered standard therapy

for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone.

Chemotherapy is generally indicated in cases refractory to reduction in immunosuppression and/or RTX and in those with aggressive disease at presentation or not amenable to surgery.

EBV donor-recipient mismatch (donor seropositive, recipient seronegative at transplant) is the most well-established risk factor for PTLD. The increased incidence of PTLD in children is attributed to their pretransplant EBV-naïve status.

85. **Answer:** A

Serum quantitative CMV assays in patients with invasive colitis and gastritis or neurologic disease including chorioretinitis are often negative. Patients suspected to have tissue-invasive CMV disease but with negative QNAT (or pp65 antigenemia) should have tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease.

Recommendations for CMV prophylaxis therapy: See text, **Table 9.21**.

Detecting CMV DNAemia on routine surveillance requires treatment even if the patient is asymptomatic. However, CMV DNA threshold to treatment may differ among centers and clinicians

86. **Answer:** A

Weight reduction

- Systolic blood pressure (SBP) may reduce by 1 mm Hg/kg weight loss.
- Pharmacologic strategies if safely tolerated (eg, orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide)

Adopt DASH-like eating plan.

- Encourage diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced saturated and total fat.
- SBP may decline by 8 to 14 mm Hg.

Sodium restriction

- Less than 1,500 mg/d; aim for 1,000 mg/d or more reduction in most adults
- SBP may reduce by 2 to 8 mm Hg.

Increase potassium intake

- 3,500 to 5,000 mg/d unless the patient has problems with hyperkalemia (eg, If feasible, use salt substitutes, KCl + NaCl combination instead of regular salt with NaCl alone)
- SBP may reduce by 4 to 5 mm Hg.

Physical activity

- Regular aerobic, dynamic resistance, or isometric resistance activity (eg, 30-minute brisk walk daily, most days of week, or 150-min/wk)
- SBP may reduce by 4 to 9 mm Hg.

Moderation of alcohol consumption

- Less than 2 drinks daily in most men, less than 1 drink daily in women and lightweight persons
- SBP may reduce by 2 to 4 mm Hg.

87. **Answer:** A

Andexanet reverses apixaban and rivaroxaban, phytonadione is vitamin K that may be used to reverse the anticoagulant effect of warfarin, protamine reverses heparin (unfractionated or low molecular weight [LMW]), and idarucizumab reverses dabigatran.

88. **Answer:** C

Secondary hPTH aims to correct an existing hypocalcemia in patients with kidney disease. Hypocalcemia leads to secondary hPTH but not vice versa.

Nephrogenic DI does not cause hypocalcemia. Although hypercalcemia can cause nephrogenic DI.

Loss-of-function mutations involving FGF-23 would increase $1,25(OH)_2$ vitamin D, which would not cause hypocalcemia.

This patient presents with severe AKI associated with severe hypocalcemia. Calcium levels typically do not drop to severely low levels within 2 weeks from AKI. The reason for acute calcium

lowering is most likely due to tissue deposition that may be seen with rhabdomyolysis or acute pancreatitis. Acute rhabdomyolysis can best explain the patient's presentation with AKI, hyperkalemia (intracellular cations released with muscle injury), severe hyperphosphatemia (intracellular anions released with muscle injury), very high creatinine, and very low calcium (deposition into injured tissues).

89. **Answer:** A

The current patient has BKPyV DNAemia. Reduction in immunosuppression remains the cornerstone in the management of BKPyV DNAemia with or without BKPyV-nephropathy.

Currently existing literature does not support the use of quinolone, leflunomide, cidofovir, or intravenous immunoglobulin (IVIG) in the management of BKPyV DNAemia. Proper randomized clinical trials are lacking to generally recommend treatment by switching from mycophenolate to mTOR inhibitor, or from tacrolimus to cyclosporine.

90. **Answer:** B

WCH refers to having home or daytime ambulatory BP less than 130/80 mm Hg but office BP greater than 130/80 mm Hg after 3 months of diet and lifestyle modification.

Some studies revealed increased left ventricular mass index with WCH. Conversion to sustained HTN occurs in 1% to 5% annually. Antihypertensive therapy is recommended if office BP is persistently elevated and with evidence of target organ damage, for example, left ventricular hypertrophy on ECG or echocardiogram. Since this is a new patient, obtaining an ECG or echocardiogram to assess for target organ damage should be done to help direct management. Although encouraging a low-sodium diet is generally advisable, this patient states that she has already done her best with maintaining a healthy lifestyle over the past 3 months.

91. **Answer:** C

Hormonal replacement in patients with panhypopituitarism can rapidly correct the associated inappropriate release of ADH

(SIADH) and cause the high-volume aquaresis within 24 hours. This aquaretic response can lead to rapid overcorrection of hyponatremia. It is vital to anticipate this response and manage accordingly. In the case of rapid aquaresis, the administration of DDAVP is required.

Chronic polydipsia and polyruria are less likely because water restriction did not correct the hyponatremia.

Undocumented infusion of 3% is possible, but less likely realistically. For her sodium to go up to 134, she must have received approximately 700 mL of 3% saline. It is unlikely that this was somehow missed.

Lab error is less likely given the trend of increasing serum sodium.

92. **Answer:** D

The patient has bilateral ankle edema and suboptimal BP control. Diuretics are ineffective in treating CCB-induced edema. Although not all CCBs can induce edema to a similar extent, switching amlodipine to nifedipine is not a good option at this time, given the patient's relatively high heart rate. Adding nifedipine can cause reflex tachycardia and easily increase her heart rate to above 90 beats per minute. Many patients do not tolerate this heart rate increase.

A β-blocker is not considered first line as an antihypertensive agent. In addition, it is generally preferred that we select the best and most simple antihypertensive combination for patients and avoid polypharmacy.

ACEis have been shown to improve CCB-induced edema via its venodilating effect. Other agents with similar benefits include ARBs and nitrates. Since the patient is only on a low-dose chlorthalidone, switching it to an ACEi or ARB is reasonable. Although not listed, another option is to switch amlodipine to an ACEi or ARB.

93. **Answer:** A

This patient has anasarca and likely significant nephroedema as well, given enlarged kidneys on ultrasound. Tissue edema involving the kidneys can reduce renal perfusion pressure and

cause a prerenal state leading to AKI. Diuresis is the best therapeutic option. Renal beneficial effects of hyperoncotic albumin infusion alone have not been consistently shown in patients with nephrotic syndrome. This patient is currently volume overloaded and does not need IV fluids. The use of renin-angiotensin inhibitors in patients with MCD is generally not suggested unless indicated for HTN. In addition, adding a renin-angiotensin inhibitor in a patient with existing poor renal perfusion may worsen the AKI.

94. **Answer:** D

The use of SPS is contraindicated in patients with bowel obstruction, ileus, and postanesthesia. In current patient with a history of constipation, SPS use is not safe. In addition, SPS has been shown to have poor efficacy, and most experts advise against its use.

Patiromer may potentially worsen the patient's underlying problem with hypercalcemia.

Sodium zirconium cyclosilicate is associated with edema and constipation that may worsen the patient's ongoing problems with volume overload and constipation.

The use of laxatives such as PEG-3350 is indicated because constipation can reduce gut potassium secretion. PEG-3350 binds water in the gut, incorporates with stool, and promotes intestinal peristalsis to improve bowel movement.

95. **Answer:** D

The reason for the rise in serum phosphate is unclear. There is no significant kidney injury (current rise in SCr could be from trimethoprim). There is no concurrent hyperkalemia or hyperuricemia to indicate any ongoing cell lysis.

In general, antibiotics are not known to cause isolated hyperphosphatemia. There is no reason to discontinue current antibiotics.

Some chemical analyzers are known to use an acidifying agent in measuring phosphate. With the use of this acidifying agent, phospholipids from liposomal amphotericin may get hydrolyzed

from the amphotericin molecule and are measured as serum phosphorus. Pseudohyperphosphatemia must be considered when there is unexplained hyperphosphatemia in a patient receiving liposomal amphotericin. This can be done by consulting with the laboratory staff.

Other conditions that can cause pseudohyperphosphatemia include heparin- or alteplase-contaminated blood sampling that contains phosphoric acid as a buffer solution, paraproteinemia (interference with measurement of phosphate or phosphate binding to paraproteins), and hyperlipidemia (presumed associated turbidity).

96. **Answer:** D

Anti-HLA antibodies are formed after exposure to allogeneic HLAs through blood transfusion, prior transplantation, and pregnancy. HLA sensitization can also develop following immune activation in patients with implantable ventricular assist devices, infections, or following a pro-inflammatory event such as surgery.

97. **Answer:** B

This patient presents with hyperventilation and severe acute respiratory alkalosis. Hyperventilation leads to extracellular CO_2 diffusion, thereby increasing intracellular pH. The increased intracellular pH promotes glycolysis and downstream adenosine triphosphate (ATP) production. ATP synthesis requires rapid cellular phosphate uptake, hence extracellular hypophosphatemia. Treatment is management of anxiety with anxiolytic to treat the underlying respiratory alkalosis.

98. **Answer:** C

In managing HTN in CKD, KDIGO 2024 suggests targeting standardized office SBP to less than 120 mm Hg, if safely tolerated.

The use of ACEi or ARB is *recommended* for individuals who are nondiabetic with high BP, CKD, and severe albuminuria (G1-G4, A3) and individuals with diabetes with high BP, CKD, and moderate-to-severe albuminuria (G1-G4, A2, and A3).

ACEi or ARB is *suggested* for individuals with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without DM.
It is recommended to avoid combination use of ACEi, ARB, and direct renin inhibitor therapy in patients with CKD, with or without DM. However, the use of an ACEi or ARB with an MRA is not contraindicated, although it should be monitored closely for adverse effects such as hyperkalemia and metabolic acidosis.
In patients with difficult-to-treat HTN, the addition of an MRA may be considered if safely tolerated.
The use of chlorthalidone has been shown to be effective even among patients with stage 4 CKD. (Agarwal R, Sinha AD, Cramer AE, et al. Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease. *N Engl J Med*. 2021;385(27)::2507-2519.)

99. **Answer:** D
APOL1 high-risk variants should not affect disease recurrence after transplant. Familial FSGS has a low recurrence rate, with the exception of NPHS1 mutation (Fin-major type). The latter has a recurrence rate of 25% to 34%. Histologic variants (collapsing, tip lesion, cellular, perihilar, not otherwise specified) have no effect on recurrence risk.

00. **Answer:** C
Per KDIGO, prophylactic pericontrast HD has been shown to be potentially harmful and is not recommended. For patients on established dialysis, immediate dialysis is not needed unless other indications exist (eg, volume overload, hyperkalemia). For the current patient, there are no volume overload signs or any life-threatening electrolyte disturbances to warrant immediate HD therapy.

01. **Answer:** C
This patient has absolute iron deficiency, defined as having a combination of ferritin less than 100 ng/mL and transferrin saturation less than 20%. Iron supplementation is indicated prior to providing an ESA for a greater response. Currently, HIF stabilizers are only approved for use in patients receiving kidney replacement therapy. There is no reason to perform a bone

marrow biopsy at this time, given relatively normal other cell lines.

02. **Answer:** D

The medical director should work with the unit staff to resolve any existing issues first. The medical director should only transfer the patient after all efforts to resolve the issue have failed. A patient cannot be discharged from a dialysis unit without assistance to transfer to another unit. Upon transfer, only medical records should be provided unless requested specifically by the accepting unit for transfer consideration. This is considered blacklisting and will be reported to the State Survey Agency.

The rationale for dismissing disruptive patient from the dialysis unit:

It is the medical director's responsibility to ensure "that no patient is discharged or transferred from the facility unless:

- The patient or payer no longer reimburses the facility for the ordered services
- The facility ceases to operate
- The transfer is necessary for the patient's welfare because the facility can no longer meet the patient's documented medical needs
- The facility has reassessed the patient and determined the patient's behavior is disruptive and abusive to the extent in which the delivery of care to the patient, or the ability of the facility to operate effectively is seriously impaired…."

03. **Answer:** D

The ALLHAT did not show any difference in coronary heart disease or nonfatal myocardial infarction and stroke among CCB, ACEI, and thiazide diuretic. All three agents are considered first-line agents in the treatment of HTN.

04. **Answer:** D

The primary defect in Liddle syndrome is gain-of-function mutation of the ENaC at collecting tubules that leads to increased sodium reabsorption, thus HTN. The sodium retention leads to

inhibition of the renin-angiotensin system, thus normal to low plasma renin and aldosterone levels. In addition, sodium retention facilitates potassium and proton secretion at collecting tubules, leading to associated hypokalemia and metabolic alkalosis. Treatment for Liddle syndrome is direct inhibition of ENaC with amiloride.

05. **Answer:** B
This patient with metastatic ovarian carcinoma presents with AKI associated with a markedly distended and tense abdomen, reduced urine output, urinalysis with hyaline casts, and elevated lactic acid levels. The clinical manifestations suggest poor renal perfusion and likely associated poor tissue perfusion. Given that this patient has been eating well, hypovolemia is less likely. The tense abdomen in a patient with intra-abdominal malignancy should raise concerns for intra-abdominal compartment syndrome. Measurement of intra-abdominal pressure is warranted. An abdominal CT will probably not be helpful in this patient with known metastatic ovarian carcinoma. Furosemide stress test is used in euvolemic to hypervolemic patients with AKI to predict the risk for severe AKI and need for KRT. There is no clinical evidence to suggest urinary retention.

06. **Answer:** D
All the options are true.

07. **Answer:** D
Abiraterone is an inhibitor of androgen synthesis used to treat metastatic or castration-resistant prostate carcinoma or androgen receptor–positive breast carcinoma. Abiraterone inhibits 17α-hydroxylase, which reduces downstream cortisol synthesis. Hypocortisolism activates adrenocorticotropic hormone (ACTH), which drives upstream synthesis of deoxycorticosterone (DOC). DOC has mineralocorticoid activity that can lead to sodium retention, hypokalemia, and HTN. This abiraterone-induced complication can be treated with eplerenone up to 200 mg/d or low-dose dexamethasone (0.5 mg/d).

08. **Answer:** D

Despite having low iron and low transferrin saturation, ferritin is significantly elevated. Because ferritin is an acute-phase reactant, significantly elevated ferritin should raise concerns for an underlying inflammatory or infectious condition and malnutrition. Iron supplementation should be held until everything has been ruled out.

Adverse effects associated with IV iron include increased oxidative stress, endothelial injury, vascular calcifications and plaque formation, and impaired leukocyte function, which may facilitate bacterial growth. The use of IV iron in patients with systemic infections is not recommended. IV iron should be held if ferritin greater than 500 ng/mL. Note, however, that even when KDOQI iron parameters have been reached, anemia may still respond to iron therapy in some patients. This is referred to as "functional iron deficiency." Clinical judgment for continuing iron supplements in these cases is required.

09. **Answer:** A

The fractional excretion of magnesium can be calculated as (FeMg) = ([Urine Mg × SCr] ÷ [0.7 × Serum Mg × Urine Cr]) × 100. The factor of 0.7 indicates only approximately 70% of plasma Mg is filterable. This equation should only be used in patients with relatively good kidney function.

Interpretation: FeMg more than 2% to 4% indicates excessive renal Mg^{2+} wasting (eg, renal causes). FeMg less than 2% to 2.5% indicates extrarenal causes of hypomagnesemia (eg, intestinal causes).

Current patient's FeMg (8 × 0.7) ÷ (0.7 × 1.5 × 89) × 100 is 6%, and 24-hour urine greater than 20 mg/d is consistent with renal magnesium wasting. This may be due to cisplatin-induced proximal tubular injury (ie, Fanconi syndrome).

This patient's hypomagnesemia is less likely due to proton pump inhibitor–induced hypomagnesemia because it is thought to be due to reduced GI absorption of magnesium; in which case, FeMg should be less than 2% to 2.5%.

In malnutrition and hypovolemia, FeMg is also expected to be low.

10. **Answer:** A

    Interferon therapy may be associated with a preeclampsia-like syndrome with thrombotic microangiopathy, new-onset headaches, severe HTN, and proteinuria. This is likely due to the anti-vascular endothelial growth factor (anti-VEGF) effect of interferon therapy. Interferon therapy can also be associated with AKI due to ATN, AIN, and glomerular diseases, including FSGS, MN, MCD, and MPGN. The most important management strategy is discontinuation of interferon therapy.

    This patient does not have thrombotic thrombocytopenic purpura (TTP) given normal ADAMTS13 activity and does not need PLEX.

    Although the patient's current presentation resembles preeclampsia, this only occurs after 20 weeks of pregnancy. The patient has a flat abdomen on examination, which makes pregnancy less likely. It is not useful to obtain a β-human chorionic gonadotropin level at this time.

    Although the patient has evidence of hemolysis (anemia, schistocytes, elevated lactate dehydrogenase), her normal coagulation studies rule out DIC.

11. **Answer:** D

    The current patient has combined respiratory acidosis and metabolic alkalosis. The high pCO_2 is likely due to a combination of her chronic respiratory acidosis from her chronic obstructive pulmonary disorder and an added CO_2 retention in response to loop-induced volume loss and metabolic alkalosis. Since the patient is still volume overloaded, more fluid needs to be removed. Acetazolamide is a diuretic that induces bicarbonaturia and ameliorates the loop diuretic–induced metabolic alkalosis and its associated CO_2 retention. Acetazolamide may be added transiently to reduce the severity of bumetanide-induced metabolic alkalosis while continuing diuresis. Noninvasive positive pressure support can help reduce the retained CO_2.

    Adding thiazide diuretic can help increase diuresis at the expense of worsening metabolic alkalosis and associated CO_2 retention.

Volume expansion with either normal saline or lactated Ringer solution in a significant volume-overloaded patient is not appropriate.

12. **Answer:** B

    The current patient's hemoglobin is already at goal. Adding an ESA or HIF stabilizer is not recommended. In addition, this patient is at increased risk for adverse effects from the use of ESAs and HIF stabilizers including increased risk for cardiovascular events and tumor progression and possibly worsening HTN including hypertensive crisis.

    Review general contraindications, warnings, and precautions common with the use of ESA and HIF stabilizer.

    Contraindications: uncontrolled HTN; contraindication for ESA specifically: pure red cell aplasia that begins after the initiation of an ESA

    Warnings and precautions: increased mortality, myocardial infarction, stroke, and thromboembolism with target hemoglobin greater than 11 g/dL; use with precaution in patients with coexistent cardiovascular disease and stroke; increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer; HTN: control HTN prior to initiation or during treatment with ESA or HIF stabilizer.

13. **Answer:** C

    Bilateral RCC in a young individual below the age of 40 should raise suspicion for a familial renal cystic disease with tumor syndromes, such as von Hippel-Lindau syndrome, tuberous sclerosis complex, or Birt-Hogg-Dubé. In this patient with a history of intermittent hypertensive episodes, pheochromocytoma (arising from adrenals) or paraganglioma (extra-adrenal in origin) (PPGL) must be ruled out. Plasma-free metanephrines (metanephrines and normetanephrines) greater than 4- to 5-fold of the upper limit of normal suggests the presence of pheochromocytoma or PPGL is highly probable (sensitivity of 97% and specificity of 93%). Plasma-fractionated catecholamines (epinephrine, norepinephrine, and dopamine) testing is less

sensitive, but levels greater than 2 times the upper limit of normal range are diagnostic. Note that although paroxysmal HTN is often described with PPGL, sustained HTN or orthostatic hypotension may also be present.

14. **Answer:** D

    This patient presents with classic signs and symptoms of excess cortisol from either Cushing disease or syndrome. Cushing disease refers to pituitary adenoma producing excess ACTH. Cushing syndrome refers to conditions where excess ACTH is produced by sources other than pituitary (eg, adrenal tumors, bronchogenic carcinoma). Clinical manifestations associated with excess cortisol state include HTN, DM, coagulopathy, cardiovascular diseases, infections, osteoporosis, and fractures. Patients may also present with rapid central weight gain, round face, fat deposition at the neck base, abdominal striae, easy bruising, and generalized muscle weakness. Cortisol has mineralocorticoid activity that manifests as HTN, hypokalemia, and metabolic alkalosis. The Endocrine Society recommends using at least two of three different screening tests: 24-hour urine free cortisol excretion, late night/bedtime salivary cortisol levels, and the 1 mg overnight DST or alternatively, the 2-mg 2-day DST. Once hypercortisolism has been established, obtain the ACTH level to determine the source, that is, ACTH dependent (pituitary, ectopic) or ACTH independent (primary adrenal). Morning cortisol measurement is typically done to evaluate for hypocortisolism associated with adrenal insufficiency.

15. **Answer:** D

    The patient has proteinuria mismatch (trace protein on urinalysis but quantified at 2.7 g/g by uPCR) and minimal albuminuria suggesting the presence of Bence Jones proteins (light chains) and absence of significant injury to the glomerular filtration barrier. The lack of albuminuria rules out conditions that would typically cause significant GBM injury, including AL amyloidosis or C3G. Although AIN could present with minimal albuminuria, the degree of proteinuria is much greater than that normally seen

with tubular injury (eg, typically <1-1.5 g/g). In addition, there is no obvious evidence of AIN such as the presence of white blood cells (WBCs) in the urinalysis (although the absence of WBCs does not necessarily rule out AIN). Myeloma kidney is also known as cast nephropathy, which results from glomerular filtration and tubular precipitation of large quantities of light chains. In this condition, AKI is due to tubular obstruction from cast formation, not from glomerular injury, thus absence of significant albuminuria.

16. **Answer:** C
    Levamisole-laced cocaine is associated with ANCA vasculitis and pauci-immune GN, TMA, rhabdomyolysis, severe vasoconstriction, HTN, and even renal infarction.
17. **Answer:** B
    Risks for higher relapse rates include:
    - Diagnosis of granulomatous polyangiitis
    - Anti-proteinase 3 antibody (PR3-ANCA) positivity
    - ANCA positivity at the end of induction or rise in ANCA titer
    - Respiratory tract involvement (ear, nose, throat)
    - More extensive disease
    - Lower serum creatinine
    - History of relapse
    - Immunosuppressive therapy: lower cyclophosphamide exposure, GC withdrawal
18. **Answer:** B
    Because potassium and phosphorus are predominantly intracellular electrolytes, any patient with persistent hyperkalemia and hyperphosphatemia should be evaluated for conditions associated with cell death such as hemolysis, rhabdomyolysis, or tissue necrosis/infarction such as bowel infarction or ongoing tumor lysis.
    Given normal haptoglobin level and stable hematocrit, hemolysis is less likely.

Ogilvie syndrome is associated with hypokalemia.

The reasonably improved blood urea nitrogen levels relative to the ongoing hyperkalemia and hyperphosphatemia with daily hemodialysis suggest something other than inadequate dialysis in a hypercatabolic state may be present and must be ruled out.

Of all conditions listed, rhabdomyolysis is the most likely cause of concurrent hyperkalemia and hyperphosphatemia. In addition, note that the total serum calcium level is also slowly decreasing, which is consistent with rhabdomyolysis, where calcium sequestration into injured tissue may occur.

19. **Answer:** D

Tolvaptan is an aquaretic that can improve fluid removal and hyponatremia. However, it has not been shown to improve long-term survival. Acetazolamide can improve metabolic alkalosis, but not hypokalemia. Acetazolamide increases renal potassium loss and can worsen hypokalemia. To determine if free water restriction is effective, we can calculate electrolyte-free water volume (EFWV) in the 24-hour urine. The amount of free water intake should be less than the urine EFWV for water restriction to be effective in improving serum sodium concentration.

EFWV is urine output × (1 − [urine Na^+ + urine K^+]/serum sodium) = 2 × (1 − [70 + 30]/125) = 0.4 L EFWV loss in urine. Fluid intake of 1 L exceeds the amount of EFW loss in the urine. The net positive free water gain would decrease, not increase, serum sodium concentration. For fluid restriction to be effective in this patient, fluid intake must be below 400 mL, which is not feasible. Free water restriction would not work in this case.

20. **Answer:** D

All of the above have been shown to be associated with increased mortality risk.

21. **Answer:** A

Unlike most other causes of hypertensive emergency, BP and heart rate reductions within 20 minutes are vital in the management of an acute aortic dissection. For an acute aortic dissection, the recommended treatment includes the

administration of an IV β-blocker (eg, esmolol, labetalol, metoprolol) to reduce the pulse to below 60/min to reduce aortic shearing. A secondary vasodilator (eg, nitroprusside, clevidipine, or nicardipine) may be added as necessary to reduce the SBP to 100 to 120 mm Hg within 20 minutes.

Hydralazine is an arteriolar vasodilator, with possible reflex sympathetic stimulation, that is, tachycardia, which could increase aortic shearing. Its use should be avoided in patients with coronary artery disease or aortic dissection.

22. **Answer:** C

Glycine per se does not cause hyponatremia. Irrigation solutions for urologic or gynecologic procedures using glycine as the solute are formulated as hypotonic solutions, for example, with osmolality of 200 mOsm/kg. The use of high volume of hypotonic glycine-containing solutions in these procedures can lead to excess water reabsorption and can cause hyponatremia.

The current patient appears anxious and may have ingested a large volume of water, but her urine osmolality greater than 200 mOsm/kg is not consistent with polydipsia. This patient's measured plasma osmolality is not much higher than that calculated, (2 × [129 + 4.2] + 16/2.8 + 112/18) = 278 mOsm/kg, which rules out pseudohyponatremia.

The remaining option of SIADH is possible because it may be associated with her acute illness. The use of hypotonic solutions including D5 containing half-normal saline and relatively hypotonic IVIG solution (258 mOsm/kg) can cause hyponatremia in the setting of high ADH state.

23. **Answer:** D

Choice A, D5-containing water cannot treat the hypovolemia due to recent salt loss with nausea and vomiting.

Choice B, normal saline (154 mmol/L of sodium) can treat the patient's hypovolemia, but not hypernatremia. The patient currently has hypernatremia with corrected serum sodium of approximately 147 mmol/L, (400 − 100) × 2.4 + 140 = 147.

Choice C, the volume of lactated Ringer given is inadequate to treat the concurrent hypernatremia. The volume of electrolyte free water (EFW) gained per liter of lactated Ringer (130 mmol/L of sodium and 4 mmol/L of potassium) for this patient can be calculated as (1 − [130 + 4]/147) = 88 mL. Assuming the patient receives 500 mL bolus + 100 mL/h × 24 h, the EFW gained is 2.9 × 88 mL = 155 mL. The free water deficit in this patient is approximately 1,500 mL. Alternatively, we can calculate expected serum sodium with choice C as follows (assuming total body volume of 30 L and no urine output): (current total sodium content + sodium content from fluids provided) ÷ (current body volume + volume of fluid provided) = (147 × 30 + 134 × 0.5 + 154 × 2.4) ÷ (30 + 2.9) = 147 mmol/L.

Choice D, half-normal saline can provide adequate free water replacement while concurrently providing NaCl to replace the salt loss in the vomitus. Assuming a body volume of 30 L, the expected sodium with choice D = (current total sodium content + sodium content from fluids provided) ÷ (current body volume + volume of fluid provided) = (147 × 30 + 77 × 2.9) ÷ (30 + 2.9) = 141 mmol/L.

24. **Answer:** D

Ecstasy (MDMA), bath salts (derivatives of cathinone, eg, methylenedioxypyrovalerone, methylone, or mephedrone), cannabis, and synthetic cannabinoids can all present with rhabdomyolysis and hyponatremia. Cocaine most commonly causes rhabdomyolysis and, in severe cases, renal infarction. Cocaine adulterated with levamisole is associated with ANCA vasculitis.

25. **Answer:** C

This patient's AKI may be due to contrast-associated AKI, hypovolemia due to osmotic diuresis associated with poorly controlled diabetes, and, possibly, poor oral intake with recent altered mental status. Given a physical examination that is consistent with reduced intravascular volume (eg, dry oral mucosa, absence of peripheral edema) and lack of evidence of

severe liver disease, it is less likely that the AKI is related to HRS. Hyperoncotic albumin and terlipressin are not indicated. Correction of hyperglycemia with insulin and volume expansion with normal saline is the best management options. Given the patient's hyperkalemia, lactated Ringer is not the best fluid option for volume expansion because it contains potassium.

26. **Answer:** B
    This patient shows signs of malnutrition, including unintentional weight loss and decreasing serum albumin levels. KRT is indicated at this time.

27. **Answer:** D
    The management of atheroembolic disease is supportive care only. In patients who develop kidney failure from atheroembolic disease, dialysis support may be provided. Anticoagulation is not recommended due to concerns for the loosening of more atheromatous plaques and worsening of atheroembolic disease with anticoagulation. Anticoagulation is required for DVT associated with nephrotic syndrome, regardless of the underlying glomerular disease and antiphospholipid syndrome. The duration of anticoagulation for the former is for the duration of the nephrotic syndrome and lifelong for the latter. Specific recommendations regarding anticoagulation in patients with ESKD and atrial fibrillation are lacking. Some experts would anticoagulate higher risk individuals based on CHA2DS2-VASc scores. Anticoagulation should be "individualized" and discussed with patients based on risks and benefits. Other options including left atrial appendage occlusion or "no therapy" may be considered based on multidisciplinary team discussion.

28. **Answer:** C
    For the current patient, urea reduction ratio (URR) per dialysis treatment is (70 − 35) ÷ 70 = 50%.
    UF rate of 3,200 mL for an 80-kg patient over 3 hours is 3,200 ÷ 80 ÷ 3 = 13.3%. Based on KDOQI recommendations for HD adequacy given 3 times/wk, this patient's solute clearance is inadequate and the UF rate of greater than 13 mL/kg/h is

associated with increased mortality. Patient needs to be advised to reduce daily fluid intake.

Review KDOQI recommendations for HD adequacy given 3 times/wk:

- For patients with residual kidney urea clearance K_r less than 2 mL/min/1.73 m^2:
  - Minimally adequate dose: single pool K_t/V (spK_t/V) 1.2 or higher per dialysis (not including K_r), or URR 65% or more
  - Target dose: spK_t/V 1.4 or more (~equilibrated K_t/V [eK_t/V] ≥1.2) per dialysis (not including K_r), or URR 70% or more
- For patients with residual kidney urea clearance K_r 2 mL/min/1.73 m^2 or more:
  - Minimally adequate dose: spK_t/V may be lower than 1.2.
  - Target dose: 15% or more of minimum dose
- The Centers for Medicare & Medicaid Services (CMS) conditions for coverage for ESKD require maintenance of spK_t/V of at least 1.2.
- Targeting K_t/V greater than 1.4 does not appear to improve survival or reduce hospitalization rates.

Dialysis duration:

- Optimal dialysis time and frequency are undefined. 2015 KDOQI clinical practice guideline recommends greater than 3 hours for patients who receive HD 3 times a week. Some experts suggest 4 hours or more.
- Dialysis session duration less than 4 hours has been associated with increased mortality and morbidity.
- Frequent HD has been suggested for patients with nutritional problems or volume overload, but current data show no benefit in terms of improved nutritional status or anemia control.

  UF rate:

  UF rate greater than 13 mL/kg/h is associated with increased mortality. UF rate less than 10 mL/kg/h is suggested.

29. **Answer:** D

IgG4-RD is a condition characterized by dense lymphoplasmacytic infiltration of predominantly IgG4-positive plasma cells and small lymphocytes in various organs. Lymphoplasmacytic infiltration can lead to the formation of mass lesions in various organs, including pancreas, autoimmune pancreatitis, enlarged (submandibular) salivary glands, kidneys (tubulointerstitial nephritis), lungs, lymph nodes, meninges, aorta (chronic sclerosing aortitis and periaortitis), breast, prostate, thyroid (thyroiditis), pericardium, skin, and even bone (destructive lesions resembling granulomatous polyangiitis). Renal involvement of IgG4-RD includes tubulointerstitial nephritis, membranous nephropathy, IgG4 plasma cell arteritis, and obstructive uropathy from retroperitoneal encasement/fibrosis. Hyperoxaluria can cause calcium oxalate stones and obstructive uropathy. Hyperoxaluria per se may also cause interstitial nephritis. Renal tuberculosis may have associated granulomatous disease and hypercalcemia. Both can cause interstitial nephritis. The formation of calcium stones can also cause obstructive uropathy. Renal tuberculosis may also be associated with papillary necrosis in rare cases, which can cause obstructive uropathy.

30. **Answer:** C

A 47-year-old female who presents with intractable nausea and vomiting and sepsis has a high serum anion gap (SAG), which could arise from a high SAG metabolic acidosis. A change in gap of 9 suggests the presence of nine excess anions, or nine acids that accompany the nine anions. The nine acids are expected to consume an equivalent nine bicarbonate, which would lower the serum bicarbonate to an expected level of 15 mmol/L. Since the actual bicarbonate is 24, which is higher than 15, we can deduce that metabolic alkalosis is also present. The only patient who could present with both a metabolic alkalosis and a high SAG metabolic acidosis is patient C. Vomiting induces metabolic alkalosis, while sepsis can cause reduced tissue perfusion, thus lactic acidosis and elevated SAG metabolic acidosis.

31. **Answer:** B

    There is nothing in this patient's laboratory studies to suggest an acute LN flare. Her disease activity serologies (complements and anti–double-stranded DNA) are within normal limits, her urinalysis is bland without any cells or casts. Despite the increase in urine protein to creatinine ratio, her albuminuria is very minimal, which suggests that an active glomerulonephritis is less likely. For these reasons, intensification or switch of her immunosuppressive therapy is not currently warranted.

    Her history of NSAIDs use may have contributed to intermittent ATN with or without AIN. Discontinuation of NSAIDs with close follow-up is warranted.

32. **Answer:** D

    HLA class I antigens are expressed on all nucleated cells. Therefore, antibodies directed against HLA class I can result in a positive crossmatch with both B and T cells. HLA class II antigens are *constitutively* expressed only on professional antigen-presenting cells (APCs), including dendritic cells, macrophages, and B lymphocytes. Therefore, antibodies directed against class II will only cause a positive crossmatch with B lymphocytes.

33. **Answer:** B

    All of the above recreational drugs can cause AKI and rhabdomyolysis. However, the presence of hyperthermia and hyponatremia suggests ecstasy as the causative agent.

34. **Answer:** B

    Initiating an insulin drip will acutely drop this patient's serum potassium to a life-threatening level. Note that although the current level of 3 mmol/L is not severely low, it actually already reflects a significant degree of extracellular shift, given the lack of insulin and extracellular hyperosmolality evidenced by a very high serum glucose level. In addition, given the history of medication nonadherence, the patient's total body potassium store is likely severely depleted. Rapid potassium intracellular shift will occur with insulin infusion. Correction of potassium to a safer level is warranted prior to initiating the insulin drip.

Bicarbonate infusion will similarly drop the patient's serum potassium level to a potentially life-threatening level. A pH of 7.22 is not generally life-threatening. Immediate bicarbonate infusion is not warranted.

Current hyperglycemia is also not immediately life-threatening. Insulin infusion can be delayed for a few hours until potassium has been replaced to a relatively safe level.

The patient currently only has mild respiratory acidosis (expected pCO_2 for current metabolic acidosis based on Winter formula is 24 ± 3 mm Hg), immediate intubation is not warranted.

35. **Answer:** B

This patient's urine is notable for very high sodium intake (354 vs <100 mmol/d daily recommended sodium intake), high uric acid, phosphorus, and calcium intake, all suggest very high dietary intake. The low citrate and normal oxalate range suggest poor vegetable/fruit intake.

Given the current 24-hour urine metabolic profile, the patient is at increased risk for uric acid stone (high uric acid level and low urine pH), calcium oxalate stone (high calcium, low citrate, high range oxalate), and, possibly, calcium phosphate stone (high calcium, high phosphorus)—low urine pH, however, is protective against calcium phosphate stones since calcium phosphate precipitates a high urine pH.

Dietary change should be recommended to this patient: increase fluid intake to achieve urine volume 2.5 to 3.0 L/d, reduce sodium intake by 2/3 of current intake, home-cooked meals with fresh vegetables and fruits without added salt, and reduce animal protein intake (dairy animal protein).

36. **Answer:** D

Plasmapheresis may be considered in patients with ANCA-associated GN with any one of the following: severe renal impairment (SCr >3.4 mg/dL), diffuse pulmonary hemorrhage with hypoxemia, or concurrent anti-GBM disease and ANCA vasculitis.

When ANCA and anti-GBM antibodies coexist, the disease course is similar to that seen in anti-GBM disease in early disease, but the relapse pattern is similar to ANCA disease.

Maintenance immunosuppressive therapy is necessary for patients with ANCA-associated GN with or without the coexistence anti-GBM.

37. **Answer:** A

Intradialytic hypotension is a common complication during HD therapy. Common conditions include excessive fluid and/or rapid solute removal, gastrointestinal blood pooling if eating during dialysis, angina equivalent, pericardial effusion, dialysate factors (use of acetate or low calcium concentrations), dialyzer reaction, warm room temperature, and air embolism.

For the current patient, her dialysate temperature is already colder than her body temperature, which should help reduce intradialytic hypotension risk.

The dialysate calcium concentration is relatively standard and not considered low. Low dialysate calcium concentration can be associated with hypotension.

Although angina equivalent should always be considered in patients with intradialytic hypotension, this option is less likely in this patient who appears to be in good shape as she has joined Zumba class and reports doing well. Her UF rate of 800 mL/h ÷ 60 kg ÷ 1.5 h = 8.9 mL/kg/h is acceptable (typically <10 mL/kg/h is suggested). Of all the options, increased dry weight is the most likely reason, particularly given the fact that the patient has been working out and eating better.

38. **Answer:** B

This patient has signs of a full bladder on examination (mildly distended abdomen and tenderness of lower abdomen—a full bladder typically presents on examination as suprapubic distention), chemistry findings consistent with obstructive uropathy including concurrent hyperkalemia and metabolic acidosis out of proportion to the degree of kidney injury, and risks for neurogenic bladder (DM and use of diphenhydramine with

anticholinergic activity). The presence of white blood cells in the urine may be consistent with AIN, pyelonephritis, or urinary stasis. AIN, however, is not typically associated with chemistry findings or physical findings described. This patient does not have constitutional symptoms related to pyelonephritis (absence of leukocytosis and fevers) to have pyelonephritis. In addition, pyelonephritis typically does not present with AKI unless severe, in which case, the patient would be expected to have more severe constitutional symptoms. Diabetic kidney disease does not present with AKI.

39. **Answer:** C

    Facial edema is a sign of central vein stenosis/obstruction. All others may be seen with downstream stenosis of the AV access. Persistent hyperkalemia without an obvious source may be a sign of poor solute clearance. Of note, a common sign of downstream stenosis of the AV access is prolonged bleeding at the puncture site at completion of HD treatment.

40. **Answer:** A

    There is no evidence of renal or cardiovascular benefits with invasive therapy compared with conservative medical therapy in individuals with stable kidney function and BP. For this reason, invasive interventions are generally not done in patients with medically controlled HTN and stable kidney function. However, invasive therapy may be considered in younger patients with low comorbidities and rapidly progressive disease (ie, significant AKI with either renin-angiotensin-aldosterone system [RAAS] inhibition or achievement of BP control), failure to achieve goal BP despite being on appropriate medical therapy, associated acute "flash pulmonary edema," and/or significant stenosis of a solitary kidney.

    Contraindications to invasive therapy include advanced kidney disease (eg, chronic kidney disease with SCr >3-4 mg/dL, kidney length <8-8.5 cm), poor surgical candidate, and low life expectancy.

A low renal arterial resistive index (ie, <0.7) suggests the absence of high vascular resistance (eg, no significant arteriolosclerosis, absence of severe endothelial swelling in AKI causing narrowing of arterial lumen). Low resistance generally indicates good arterial flow, thus presumed low level of damage to the arterial system. High resistive index may indicate advanced arteriolosclerosis associated with renal artery stenosis, in which case, repair/angioplasty of the renal artery stenosis is of low yield for BP improvement.

41. **Answer:** B

The current patient presents with hypertensive emergency with evidence of ongoing end-organ damage (papilledema, AKI, microscopic hematuria) but without evidence of acute aortic dissection, stroke, or intracranial hemorrhage. Recommendations for BP lowering are as follows:

Gradual BP reduction is *generally* recommended: mean arterial pressure reduction by approximately 10% to 20% in the first hour, then by an additional 5% to 15% over the next 23 hours, for a total 24-hour BP reduction less than 25%.

Exceptions to gradual BP reduction over the first day

1. Acute phase of ischemic stroke: BP NOT lowered unless 185/110 mm Hg or more in candidates for reperfusion therapy; for nonreperfusion therapy candidates, BP should NOT be lowered unless 220/120 mm Hg or more.
2. Acute aortic dissection: SBP should be lowered to target of 100 to 120 mm Hg *within 20 minutes* and heart rate reduced to less than 60 beats per minute to reduce aortic shearing.
3. Acute intracranial hemorrhage: For SBP between 150 and 220 mm Hg, acutely lowering SBP to 140 mm Hg is suggested. For SBP greater than 220 mm Hg, aggressive SBP lowering to 140 to 160 mm Hg is reasonable. For all hypertensive emergencies, keep the patient euvolemic to reduce further renin angiotensin aldosterone system activation.

42. **Answer:** A

The use of mTOR inhibitor is effective in both primary and secondary skin cancer prevention. Meta-analyses and randomized trials evaluating mTOR inhibitor use in secondary prevention of SCC showed a reduction in cumulative tumor load, suggesting that most benefit is gained by early conversion to an mTOR inhibitor–based maintenance regimen.

Whereas BCC is the most common type of skin cancer in the general population, SCC has been reported to be 2 to 5 times more common than BCC in recipients of solid-organ transplantation.

Common cancers in the general population, including breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some but not all studies.

43. **Answer:** B

Ciprofloxacin crystals take the form of needles, stars, or fan-shaped crystals. Risks for crystallization and associated AKI include older age and having urine pH greater than 7.0. The current patient has high urine pH from using potassium citrate for uric acid stone. It is vital to monitor urine pH when using an alkalinizing agent. High urine pH greater than 6.5 can also increase the risk of calcium phosphate stone precipitations. Use ciprofloxacin with care when used concurrently with an alkalinizing agent. Uric acid does not crystallize at high urine pH (eg, pH >6.0).

44. **Answer:** A

A water loading test is performed to confirm a suspected diagnosis of SIADH in patients with hyponatremia.

A water deprivation test may be performed in patients with aquaresis to evaluate for diabetes insipidus (DI). The water deprivation portion is only needed when the patient's serum osmolarity is below 298 mmol/L. Our patient's serum osmolarity already exceeds this level.

The patient's total daily solute load is approximately 450 to 800 mOsm/d (1.5-2.0 L of urine with osmolality ranging from 300 to

400 mOsm/kg). This is in line with an average diet (10 mOsm/kg/d). The patient does not have an osmotic diuresis. Reducing feeding is not necessary.

Despite having hypernatremia, the patient continues to have relatively high urine volume. The urine osmolality ranging from 300 to 400 mOsm/kg may be consistent with partial central or nephrogenic DI. Failure to respond to DDAVP rules out central DI. This means the patient may have partial nephrogenic DI. A copeptin level above 21.4 pmol/L can confirm the diagnosis of nephrogenic DI.

45. **Answer:** C

CSW and SIADH are very similar in terms of neurohormonal changes including stimulated ADH (copeptin) and the RAAS. Both conditions also have increased uric acid secretion and low serum uric acid level. The major clinical difference is volume status and response to saline infusion. Patients with CSW tend to present with hypovolemia, whose hyponatremia improves with normal saline infusion, whereas for those with SIADH, whose urine osmolality exceeds their plasma osmolarity, normal saline infusion may worsen the existing hyponatremia.

46. **Answer:** D

Management of metformin-induced lactic acidosis involves supportive care and alkalinization with sodium bicarbonate to maintain pH above 7.15 until the acute toxicity resolves. HD is *recommended* in the setting of chronic use or acute overdose if any of the following is present: lactate level greater than 20 mmol/L, severe metabolic acidosis (pH ≤7.0), or medical treatment failure (as determined by pH, lactate levels, or clinical status within 2-4 hours), despite appropriate supportive care and bicarbonate therapy. HD *may be considered* if any of the following is present (limited evidence): lactate levels between 15 and 20 mmol/L, metabolic acidosis (pH 7-7.1), and the presence of comorbidities (eg, shock, kidney injury, liver failure, or decreased level of consciousness).

Indications for lithium: lithium level greater than 3.5 to 4 mEq/L, or lithium level greater than 2.5 mEq/L with CNS manifestation (altered mental status, seizures, coma); impaired renal excretion, or hemodynamic instability; or lithium level between 2.5 and 3.5 mEq/L in asymptomatic patients with increasing levels or in patients with ESKD

Indications for aspirin: serum level greater than 90 to 100 mg/dL or lower if the presence of AKI, pulmonary edema, or altered mental status

Indications for ethylene glycol: ethylene glycol level greater than 50 mg/dL in the setting of severe metabolic acidosis or end-organ damage (eg, AKI or visual disturbances). Monitor levels 2 hours postdialysis to assess for rebound.

47. **Answer:** D

Hyperkalemia is often observed in fasting blood draws (eg, early morning preoperative blood draw) in patients with type 2 diabetes. This is thought to be due to the lack of endogenous insulin secretion with fasting. To correct this hyperkalemia, administer 5% dextrose-containing solutions ± insulin depending on the degree of hyperglycemia.

48. **Answer:** A

Pseudohypokalemia may be seen in patients with acute (or chronic) myeloid leukemia due to continuing cellular K^+ uptake into rapidly proliferating cells even after the blood is drawn. There may also be associated pseudohypoglycemia and hypophosphatemia.

Pseudohyperkalemia may be associated with thrombocytosis. For every 100,000 platelets/μL, serum K^+ can increase by approximately 0.15 mmol/L because K^+ moves out of platelets after clotting has occurred in test tube. Diagnosis: obtain plasma [K^+] (ie, [K^+] measured from blood sample collected in heparin-containing tube to avoid clotting process). If serum [K^+] (ie, [K^+] measured in nonanticoagulated blood) is greater than *plasma*[K^+], that is, *S*[K^+] – *P*[K^+] greater than 0.3 mmol/L, pseudohyperkalemia is likely present.

Gitelman syndrome is associated with hypokalemia, metabolic alkalosis, and normotension.

Gordon syndrome is associated with gain-of-function mutation of the sodium chloride cotransporter (NCC) and associated HTN, hyperkalemia, and metabolic acidosis. Hyperkalemia in Gordon syndrome is due to reduced renal secretion due to limited sodium delivery to collecting tubules and reduced renin-angiotensin activity. Recall that both tacrolimus and CSA may present with similar clinical manifestations due to increased expression of NCC. The treatment of HTN in Gordon is direct inhibition of NCC, which is thiazide.

49. **Answer:** A

Zero-mismatched kidneys are shared nationally because allograft survival has been shown to be superior to all other match grades. Higher cPRA scores indicate increasing difficulty in getting a kidney with a negative or acceptable crossmatch. In the current UNOS allocation system, only very highly sensitized kidney transplant candidates with cPRA of 99% to 100% are eligible for national sharing of donor offers.

50. **Answer:** A

Abiraterone is an inhibitor of androgen synthesis used to treat metastatic or castration-resistant prostate carcinoma or androgen receptor–positive breast carcinoma. Abiraterone inhibits 17α-hydroxylase, which reduces downstream cortisol synthesis. Hypocortisolism activates ACTH, which drives upstream synthesis of deoxycorticosterone (DOC). DOC has mineralocorticoid activity that can lead to sodium retention, hypokalemia (due to increased potassium secretion via the renal outer medullary potassium channel), and HTN. This abiraterone-induced complication can be treated with eplerenone up to 200 mg/d or low-dose dexamethasone (0.5 mg/d).

Eplerenone and finerenone are mineralocorticoid receptor antagonists that inhibit tubular potassium secretion.

Barbiturate coma therapy with thiopentone (to reduce intracranial pressure, eg, for traumatic brain injury) can induce intracellular

potassium uptake, causing severe hypokalemia (eg, serum potassium <2 mmol/L). Rebound hyperkalemia (eg, serum potassium >6 mmol/L) may occur during thiopentone withdrawal. Thiopentone does not directly increase tubular potassium secretion. Potassium supplement during severe hypokalemia may be necessary but at less than 100 mmol total has been suggested to prevent severe rebound hyperkalemia during thiopentone withdrawal. Slow tapering of thiopentone over 12 to 24 hours has been suggested to minimize rebound hyperkalemia.

51. **Answer:** B

Rhabdomyolysis would present with hyperkalemia and urinalysis with positive blood but without RBCs. Stone passage could cause gross hematuria if it is a large stone, in which case, there should pain related to the stone, that is, severe flank pain or pain radiating to groin depending on the location of the stone. AIN typically presents with sterile pyuria, but AIN can also present with gross hematuria. However, the current patient has no clinical history to suggest AIN. She denies taking any newly prescribed or herbal medications. ARN is the most likely cause of her AKI. Her risks of ARN include the use of warfarin, INR greater than 3, and the presence of CKD. Kidney biopsy of ARN would reveal renal tubules packed with RBCs that can cause tubular obstruction and AKI. ARN may also be seen with the use of direct oral anticoagulants.

52. **Answer:** C

KDIGO AKI Clinical Practice Guidelines: 5.8.4: We recommend delivering an effluent volume of 20 to 25 mL/kg/h for CKRT in AKI (*1A*). This will usually require a higher prescription of effluent volume (*not graded*).

Option C provides CVVHD at a total effluent flow rate of 23 mL/kg/h: dialysate 1,800 mL/h divided by 80 kg = 23 mL/kg/h.

Incorrect Answers:

Option A provides an adequate dose but the filtration fraction (FF) is over 25%, so the circuit has a high likelihood of clotting.

- Dose = 2,000 mL/h divided by 80 kg = 25 mL/kg/h

- FF = Total UF rate/plasma flow rate = 2,000/([1 – HCT] × blood flow rate [BFR]) = 2,000 mL/h/(0.7 × 6,000 mL/h) = 48%.
  Option B provides an inadequate dose: 1,000 mL/80 kg = 13 mL/kg/h.
  Option D provides an inadequate dose: 1,200 mL/80 kg = 15 mL/kg/h.

53. **Answer:** E
    Bevacizumab is an anti-VEGF agent that can induce endothelial injury and disruption of glomerular filtration barrier and lead to clinical manifestations similar to preeclampsia, including proteinuria, HTN, AKI, and TMA. Cetuximab and panitumumab (anti-epidermal growth factor receptor antibodies) are associated with hypomagnesemia.

54. **Answer:** D
    The patient's ionized calcium is high and so the calcium infusion needs to be decreased.
    Decreasing the calcium infusion rate will also result in a decrease in the circuit-ionized calcium, making citrate more effective (ideal circuit-ionized calcium for anticoagulation should be between 0.25 and 0.4 mmol/L).
    Incorrect Answers:
    Option A is incorrect because the CKRT circuit-ionized calcium is 0.42 mmol/L and decreasing the citrate rate will lead to subtherapeutic anticoagulation.
    The ideal CKRT-ionized calcium for anticoagulation is less than 0.4 mmol/L. Citrate has practically no effect if the circuit-ionized calcium is greater than 0.55 mmol/L.
    Decreasing the citrate rate will not correct the patient's high ionized calcium level. Furthermore, there is no evidence of citrate accumulation. The ratio of total to ionized calcium is 11.1/5.9 = 1.9 (converting to same units).
    Option B is incorrect because the CKRT circuit-ionized calcium is in the acceptable therapeutic range; increasing the citrate rate

will increase the citrate load to the patient and cause worsening metabolic alkalosis.

Option C is incorrect because the patient's ionized calcium is already elevated.

55. **Answer:** B

The histopathology described is consistent with membranoproliferative glomerular pattern of injury. The presence of both C3 and Igs rules out C3G. C3G should only present with C3 dominant staining, not other Igs.

Chronic active viral infections, autoimmune diseases, or lymphoproliferative disorders can present with MPGN pattern with both C3 and Ig staining on immunofluorescence microscopy. The presence of tubuloreticular inclusions may be seen in LN, viral infections, and the presence of interferon.

IgAN should stain for IgA on immunofluorescence microscopy.

ANCA-associated GN should have very minimal, if any, complement or Ig deposits on immunofluorescence, hence the general term "pauci-immune" for ANCA-associated GN.

56. **Answer:** B

Significant ingestion of methanol, ethylene glycol, and propylene glycol can cause an elevated anion gap metabolic acidosis and high osmolal gap greater than 10 mOsm/kg. Isopropanol is metabolized to acetone by alcohol dehydrogenase. Since acetone is not an anion or an acid, isopropanol ingestion does not cause an elevated anion gap metabolic acidosis. The acetone can be measured as positive "ketones" in either serum or urine. Low or absent serum ketones by the nitroprusside test after 2 hours from the time of ingestion in the absence of alcohol dehydrogenase inhibition (eg, concurrent ethanol ingestion or use of fomepizole) essentially rules out isopropanol ingestion.

57. **Answer:** B

This patient may have reduced dialysis efficiency due to cardiopulmonary recirculation from his poor ejection fraction. If he can safely undergo surgery for the creation of an AV fistula, his clearance would improve.

Using a dialysate with higher sodium concentration can improve solute clearance at the expense of greater sodium retention followed by increased water intake and subsequent volume overload in this anuric patient with HF.

Using a dialysate with reduced osmolality would reduce the concentration gradient difference across the dialysate and blood, which would result in lower solute clearance. Getting dialysis 4 times a week would increase his K_t/V but is not a practical long-term solution.

For HD, the greater the following factors, the greater the deficiency: membrane surface area, KoA and K_{uf} of membrane, duration of dialysis, dialysate flow rate (Q_d), BFR (Q_b), vascular access flow (Q_a), and concentration gradient difference of solute between dialysate and blood.

Scenarios where dialysis efficiency can be reduced include access recirculation or cardiopulmonary recirculation in patients with lower cardiac output when dialysis is done through a CVC.

High-efficiency HD refers to dialyzing through standard cellulosic membranes with large surface areas, whereas high-flux and super high-flux HD refer to performing HD using noncellulosic membranes with larger porosity, hence increased permeability to large-middle molecules, for example, β-2-microglobulin.

58. **Answer:** C

In a study exploring the incidence and mechanisms of hyperkalemia in 779 serum samples from 33 patients on PD for 1 to 59 months, Elliott et al observed hyperkalemia 3 times the frequency of hypokalemia. High-potassium diet, PD noncompliance, increased muscle mass, potassium shifts, and/or the daytime period without PD are thought to contribute to hyperkalemia. Suggested maneuvers to prevent or reverse hyperkalemia include ensuring PD compliance, adding a daytime dwell(s) to nighttime cycles to minimize the duration of empty peritoneum for hyperkalemia to develop, monitoring K diet and level closely, and adding oral sodium bicarbonate therapy to prevent or correct metabolic acidosis to minimize extracellular

potassium shift. (Elliott AB, Soliman KMM, Ullian ME. Hyperkalemia in chronic peritoneal dialysis patients. *Ren Fail*. 2022;44(1):217-223.)

59. **Answer:** D

Clearance is dependent on the rate of effluent and is improved by anything that increases effluent generation rate. Answer D has the highest effluent rate of 4 L/h.

Incorrect Answers:

A. Partitioning RF in CVVH may be done prefilter, to prevent clotting, or postfilter, to theoretically improve clearance. However, clearance would be minimally improved when compared to D. Patient has insufficient clearance.

B. Given the slow effluent rate compared to BFR, complete equilibration of small solute concentration between blood and RF occurs. Thus, increasing blood flow to 300 mL/min would not improve clearance significantly.

C. Changing from CVVH to CVVHD with the same rate of dialysate and UF would not affect clearance significantly.

60. **Answer:** B

The Endocrine Society Clinical Practice Guideline recommends confirmatory testing such as salt loading prior to performing an imaging study or more invasive testing *unless* patients present with undetectable plasma renin activity level, plasma aldosterone concentration (PAC) greater than 20 ng/dL, and spontaneous or diuretic-induced hypokalemia. In the current patient with high suspicion for primary aldosteronism (PA), confirmatory testing with salt loading was done. The result showed that the aldosterone level was not suppressible with salt loading. The next step is to perform an imaging study. If surgery is considered based on CT imaging, adrenal vein sampling for evidence of increased aldosterone levels on the suspected side should be done prior to surgery. Genetic testing should be considered in patients with PA onset at a young age (eg, <20 years old), family history of PA, or strokes at a young age (eg, <40 years old).

61. **Answer:** A

There is no indication for immediate kidney replacement therapy (KRT). Available data have not shown survival benefits with early start KRT. Watch-and-wait approach is likely preferred in this young otherwise healthy individual with good recovery potential from severe ATN.

62. **Answer:** D

Rope-ladder technique refers to rotating cannulation sites for HD access. Buttonhole technique refers to needling at the same site for HD access.

Rope-ladder cannulation is "recommended" over buttonhole technique for AV fistula and "suggested" for polytetrafluoroethylene grafts.

Rope-ladder technique is also thought to minimize the risk of aneurysm/pseudoaneurysm formation compared with buttonhole technique.

Buttonhole technique is presumed to be easier with lower pain scores with prolonged use due to the development of a skin "tract" or buttonhole. However, there may be an increased rate of infections with the buttonhole technique, presumably due to poor cleaning techniques and/or failure to remove scabs prior to cannulation.

63. **Answer:** C

This patient has thrombotic microangiopathy (thrombocytopenia, hemolytic anemia, end-organ damage [kidney injury, change in mentation/word finding problem]). Disseminated coagulopathy (DIC) is ruled out because of relatively normal coagulation studies. Diarrhea-related hemolytic uremic syndrome (HUS) is less likely, given the absence of diarrhea and any clinical history that would suggest the development of Shiga toxin–associated HUS.

After ruling out DIC and diarrheal HUS, the two remaining concerning diagnoses include thrombotic thrombocytopenic purpura (TTP) versus complement-mediated HUS. Based on the history and laboratory studies and PLASMIC score of 6, the diagnosis of TTP should be strongly considered. Although either complement-mediated HUS or TTP is possible, immediate

empirical PLEX is critical pending testing for ADAMTS13 activity level because TTP can be fatal with delayed therapy.

It is unlikely that you are expected to know how to calculate PLASMIC score on the board exam, but it is good to be familiar with the calculation and interpretation of the score. For your convenience, see below.

The PLASMIC score may be used to predict the likelihood of having TTP in patients who present with thrombocytopenia (platelets <150) and evidence of microangiopathic hemolytic anemia (MAHA), that is, schistocytes on peripheral smear. PLASMIC score relies on Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, Creatinine.

- +1 point is given for each of the following if present:
  - Platelet count less than 30×10^9/L, +1
  - Evidence of hemolysis (reticulocyte count >2.5%, undetectable haptoglobin, or indirect bilirubin >2.0 mg/dL [34.2 µmol/L]), +1
  - Absence of active cancer, +1
  - Absence of stem-cell or solid-organ transplant, +1
  - Mean corpuscular volume less than 9.0×10^{-14} L (<90 fL), +1
  - INR less than 1.5, +1
  - SCr less than 2 mg/dL (176.8 µmol/L), +1
- Risk of having severe ADAMST13 deficiency, that is, activity level less than 15%
  - Score 0 to 4: 0% (low risk)
  - Score 5: 6% (intermediate risk)
  - Score higher than 5: 72% (high risk)

64. **Answer:** B

Discontinuation of lithium along with the use of a thiazide diuretic can be done to reduce aquaresis associated with lithium-induced nephrogenic DI. However, this patient continues to need lithium.

Amiloride can block reabsorption of lithium into collecting tubules and prevent tubular damage that can lead to nephrogenic DI.
DDAVP is used for patients with central DI who lack ADH.
Tolvaptan is an ADH receptor antagonist that is used for patients with dysregulated ADH such as HF and syndrome of inappropriate release of ADH.

65. **Answer:** A
Clearance of a drug is calculated as:
Clearance = drug extraction ratio × blood flow where extraction ratio = (predialysis concentration − postdialysis concentration) ÷ predialysis concentration
In this patient, drug extraction ratio = (60 − 30) ÷ 60 = 0.5 (the value of 0.5 means 50% of the drug is "extracted" from the plasma with HD).
Clearance of drug = blood flow × extraction ratio = 400 × 0.5 = 200 mL/min

66. **Answer:** D
Plasma exchange (PLEX) should be initiated pending ADAMTS13 activity test results. Plasma replaces defective protease activity. PLEX, as compared with plasma infusion alone, may offer the additional advantage of removing ADAMTS13 antibodies.
Adjunctive glucocorticoid therapy may have added benefits in patients with autoimmune forms of TTP by inhibiting the production of anti-ADAMTS13 autoantibodies.
Rituximab (RTX), an anti-CD20 monoclonal antibody, should be considered in refractory or relapsing immune-mediated ADAMTS13 deficiency. RTX has also been used to prevent relapses in patients with autoantibodies.
Caplacizumab is a **monoclonal antibody fragment (nanobody)** that binds to **von Willebrand factor (vWF)**, thereby **inhibiting platelet adhesion and microvascular thrombosis.** Caplacizumab *does not* affect the production of anti-ADAMTS13 autoantibodies. Caplacizumab was FDA approved in 2019 for use in acquired TTP in conjunction with PLEX and immunosuppressive therapy.

67. **Answer:** A

Management of lithium overdose

Patients may present with hemodynamic instability, altered mental status, prolonged QT interval, arrhythmias, and/or kidney injury. Signs and symptoms of lithium toxicity may not correlate well with lithium levels.

Lithium is highly dialyzable due to its low molecular weight and low protein binding. Recall the indications for dialysis:

- Lithium level greater than 3.5 to 4 mEq/L, or
- Lithium level greater than 2.5 mEq/L with central nervous system manifestation (altered mental status, seizures, coma), impaired renal excretion, or hemodynamic instability
- Between 2.5 and 3.5 mEq/L in asymptomatic patients with increasing levels or in patients with ESKD

Note: Rebound is a common problem following dialytic cessation because chronic Li accumulation in body compartments other than the intravascular volume can be released into the blood. Prolonged or continuous dialysis is recommended. Close postdialysis level monitoring (eg, q6h) is necessary.

68. **Answer:** B

This patient appears to be resistant to steroid therapy for her presumed MCD. A repeat kidney biopsy is warranted to rule out the possibility of misdiagnosis for FSGS from the first biopsy. Recall that the diagnosis of FSGS often requires at least 20 glomeruli to achieve diagnosis accuracy. Further therapy depends on the correct diagnosis of the underlying glomerular disease.

69. **Answer:** C

Tenofovir, abacavir, didanosine, and cisplatin can all cause Fanconi syndrome and nephrogenic DI. Lamivudine has not been reported to cause nephrogenic DI.

70. **Answer:** C

Gitelman and Bartter syndromes should have urine sodium and chloride greater than 20 mmol/L because these conditions are equivalent to taking diuretics. At baseline, patients with these

syndromes are euvolemic and should not have low urine sodium and chloride.

In acute vomiting, urine sodium is typically greater than 20 mmol/L because it accompanies the negatively charged bicarbonate (formed from vomiting H^+) that is filtered into tubular lumen. Urine chloride can be low in association with hypovolemia from vomiting. The high bicarbonate level in the urine would give a high urine pH, typically greater than 6.5.

In ketoacidosis, urine sodium is high because the positively charged sodium accompanies the negatively charged ketoacids. The low urine pH (≤6.5) suggests low bicarbonate in the urine, which implies the anion in question is a nonreabsorbable anion, which is a ketoacid in this case.

71. **Answer:** D

Although the patient likely needs some degree of fluid resuscitation, she is currently altered and in oliguric kidney failure. Drug clearance will be delayed pending renal recovery. Given the patient's altered mental status and high salicylate level, rapid drug removal with HD is warranted.

Review the management of salicylate intoxication and indications for HD.

- Consult toxicology.
- Airway protection, mechanical ventilation as needed
- Fluid resuscitation with D5 150 mmol/L of sodium bicarbonate solution. Dextrose treats any potential CNS hypoglycemia and bicarbonate corrects the metabolic acidosis.
- Correct other electrolytes as needed, in particular, hypokalemia.
- HD indications: severe acidosis or hypotension despite fluid resuscitation, salicylate levels greater than 100 mg/dL, mechanical ventilation, and/or end-organ injury (eg, seizures, rhabdomyolysis, kidney failure, pulmonary or cerebral edema)

72. **Answer:** C

Hypovolemia-induced hyperaldosteronism is not associated with renal potassium loss because there is no sodium delivery distally for potassium exchange/secretion to occur.

Ongoing loop diuretic use is expected to show a higher serum bicarbonate level than 22 mmol/L.

Alcoholism can be associated with alcohol myopathy where patients may be more prone to developing rhabdomyolysis. In the case of rhabdomyolysis, patients should present with hyperkalemia, not hypokalemia.

Hypokalemic periodic paralysis (HPP) is a rare condition that can be precipitated by vigorous exercise, stress states, or high-carbohydrate meals. Serum potassium levels can be severely low (ie, <2 mmol/L) during an acute attack, but return to normal range in between attacks. HPP is thought to be caused by abnormal potassium influx related to sodium and calcium channelopathy associated with mutations of CACNA1S and SCN4A, respectively, resulting in hypokalemia. Affected patients may present with mild fatigue, paralysis, constipation, and arrhythmias. The diagnosis may be made with electromyography and muscle biopsy with provocative testing. Treatment during acute attacks includes potassium supplement (with caution because rebound hyperkalemia can occur with rest) and supportive care. Preventive therapy includes advice for low-carbohydrate diet, avoidance of excessive exertion, and use of spironolactone and/or acetazolamide. This condition must be differentiated from thyrotoxic periodic paralysis (TPP) with thyroid function where patients present with thyroid function consistent with hyperthyroidism, that is, low thyroid-stimulating hormone and high T3 and T4. TPP has the highest incidence in Asian males. Preventive therapy involves the treatment of hyperthyroidism and use of propranolol.

Abdelmasih R, Abdelmaseih R, Hasan M, Nasser H. A case of hypokalemic periodic paralysis in a young athlete. *Cureus*. 2021;13(5):e15236.

73. **Answer:** B

Hypophosphatemia can be seen in 40% to 90% of patients after transplant due to FGF-23– and hPTH-induced renal phosphate wasting. Elevated FGF-23 levels more strongly correlate with hypophosphatemia than hPTH.

Metabolic acidosis, but not metabolic alkalosis, stimulates phosphaturia as phosphate serves as a titratable acid.

Other potential etiologic factors of post-transplantation hypophosphatemia include glucocorticoids (via inhibition of intestinal sodium-phosphate transporter activity), mTOR inhibitors (mechanism not well defined), massive initial diuresis, defective renal phosphate reabsorption due to ischemic injury, glucosuria (due to hyperglycemia-induced osmotic diuresis), and reduced intestinal phosphate absorption (due to reduced calcitriol related to elevated FGF-23 level).

74. **Answer:** C

Patient's BP improved with passive leg raising testing. This suggests fluid responsive status. Fluid challenge is indicated, particularly when there is no evidence of fluid overload and life-threatening electrolyte disturbances now.

75. **Answer:** C

Licorice ingestion is associated with cortisol accumulation because licorice inhibits 11β-hydroxysteroid dehydrogenase, an enzyme that metabolizes cortisol to cortisone. This patient's 24-hour urine cortisol level is in the low normal range, which rules out licorice ingestion. Additionally, patients with licorice ingestion should have low or low normal renin and aldosterone.

Dexamethasone-suppressible hyperaldosteronism should have elevated plasma aldosterone level and relatively suppressed plasma renin activity. The current patient has elevated aldosterone level and increased plasma renin activity, thus rules out dexamethasone-suppressible hyperaldosteronism.

Gain-of-function mutation of the mineralocorticoid receptor should present with low to normal renin and aldosterone.

Unilateral renal artery stenosis may present with high renin and high aldosterone levels. Of note, bilateral renal artery stenosis

generally presents with volume overload and suppressed renin and aldosterone.

76. **Answer:** C

Citrate concentration in the blood is dependent on blood flow. The optimal concentration of citrate in the blood associated with adequate anticoagulation is 3 to 5 mmol/L or postfilter ionized calcium less than 0.35 mmol/L. Increasing the BFR decreases the citrate concentration in the blood, resulting in a subtherapeutic citrate level and, therefore, clotting of the circuit.

Incorrect Answers:

Option A is incorrect because the dialysis catheter is in the cavoatrial junction, which is the appropriate location for providing adequate flows.

Option B is incorrect because the FF is 12% and clotting of the circuit is associated with FF more than 20% to 25%. Increasing the blood flow decreases FF. The FF prior to the increase in blood flow was: 1,000 mL/h/([120 mL/min × 60 min/h] × [1 − 0.3]) = 20%.

Option D is incorrect because dose does not impact clotting of the circuit. Furthermore, the dose is adequate (effluent rate mL/h/weight kg) = 2,500 mL/h/90 kg = 28 mL/kg/h (adequate is between 20 and 25 mL/kg/h with guidelines suggesting 25-30 mL/kg/h to take into account down time of CKRT device).

77. **Answer:** C

Inhibitors of VEGF can induce HTN and associated vascular complications resembling preeclampsia. Venlafaxine is an antidepressant that may be associated with HTN. The mechanism of venlafaxine-induced HTN is thought to be via increased levels of norepinephrine and subsequent potentiation of noradrenergic neurotransmission. The long-acting formulation of venlafaxine increases BP in approximately 3% of patients when normal doses (75-150 mg) are used. COX-2 inhibitors have the same renovascular side effects as NSAIDs, including sodium retention and HTN. Endothelin receptor antagonists reduce BP not cause HTN.

78. **Answer:** A

Review water treatment for HD:

The required steps in water purification include carbon filtration and reverse osmosis.

Carbon filtration removes chlorine and chloramine (added to municipal water) and organic contaminants. Chloramine can cause hemolysis. Carbon filtration is done prior to reverse osmosis (see below) because chlorine and chloramine can damage the membrane used in reverse osmosis.

Softeners (optional if hard water to protect reverse osmosis membrane) exchange calcium and magnesium ions for sodium ions. Adding softeners prior to reverse osmosis may be done to protect the reverse osmosis membrane. Accumulation of calcium and magnesium can cause fouling of osmosis membrane.

Reverse osmosis is a process whereby water is forced across a semipermeable membrane by a high-pressure system. Reverse osmosis removes dissolved inorganic elements, including metal ions (ie, zinc, fluoride, copper, aluminum, arsenic), salts, chemicals, organic elements, bacteria, viruses, and endotoxins.

Deionization further removes residual ions by exchange of resins made up of both cations and anions (eg, hydrogen and hydroxyl ions, respectively) to exchange for negatively and positively charged ionic contaminants, respectively, following reverse osmosis.

- Close monitoring of the product water-specific resistivity or conductivity is required to detect changes consistent with depletion of resins. Depletion of resins can cause the release of previously removed ions such as *fluoride and may result in acute toxicity and death*. Chronic fluoride exposure can contribute to osteodystrophy.
- Note that the deionizer provides a good milieu for bacterial proliferation. An extra step for bacterial control is needed.

Ultrafilter/endotoxin filter is an optional step used to remove any residual bacteria and endotoxins.

79. **Answer:** C

Gordon syndrome, also known as pseudohypoaldosteronism type II, is associated with increased activity of the sodium chloride cotransporter (NCC) in distal convoluted tubules and secondary suppression in the renin-angiotensin system. Patients with Gordon syndrome typically present with hyperkalemia and metabolic acidosis. This condition may be treated with thiazide diuretics. Of note, calcineurin inhibitors may also increase the expression of NCCs and present with HTN in association with hyperkalemia and metabolic acidosis. Similarly, treatment is the use of thiazide diuretics.

80. **Answer:** C

Sjögren syndrome may be associated with chronic interstitial nephritis, manifested as a slow rise in SCr, relatively bland urinalysis, and low-level proteinuria without significant albuminuria. The absence of significant albuminuria and the presence of a bland urine are not consistent with glomerular disease. Of note, Sjögren syndrome is also associated with distal RTA type 1, where patients may also have associated nephrocalcinosis.

81. **Answer:** C

Tolvaptan blocks vasopressin receptor, thereby inhibiting aquaporin expression and water reabsorption at collecting tubules. Tolvaptan is essentially medication-induced nephrogenic DI. Adverse effects of tolvaptan include transaminitis, severe hepatocellular toxicity, polyuria, volume depletion, renal potassium wasting, thirst, and hyperuricemia (rarely gout). Drug interactions must be reviewed in patients taking tolvaptan because tolvaptan is a CYP3A4 substrate.

82. **Answer:** D

Patients with polydipsia will develop a "washout" medulla that can no longer effectively reabsorb water, even when the patient abruptly stops drinking. For this reason, these patients will continue to produce high volume of a dilute urine when they are placed on a strict fluid restriction. Overcorrection of hyponatremia can occur rapidly.

3% saline is not indicated in this patient because there are no life-threatening neurologic signs and symptoms of hyponatremia.
Although DDAVP may be needed when the patient's urine output exceeds the patient's ability to keep up with fluids and/or rapid overcorrection of hyponatremia occurs, it is premature to administer DDAVP at this time. Premature DDAVP administration in a polydipsic patient may worsen the existing hyponatremia, particularly if the patient continues to drink water excessively.
A conservative approach may be to reduce fluid intake gradually to allow the patient to self-correct without the administration of any medications. Concurrent increase in solute intake/load may help reduce water reabsorption by collecting tubules while allowing the kidneys to regenerate the medullary concentration gradient.

83. **Answer:** B
Isopropyl alcohol is metabolized to acetone. The presence of acetone can be detected as positive ketones in the blood. However, acetone is not an acid and does not cause a drop in serum bicarbonate. Acetone is also not an anion and does not cause an elevated anion gap. The presence of any exogenous alcohol can increase serum osmolality, thus the presence of an increased serum osmolality gap. Isopropyl alcohol intoxication can cause CNS suppression, nausea, and vomiting. The management of isopropyl alcohol intoxication is supportive care and airway protection. hemodialysis may be considered for refractory and severe hemodynamic instability in association with blood levels greater than 500 mg/dL and serum osmolar gap greater than 100 mOsm/L.

84. **Answer:** D
AME syndrome is associated with reduced conversion of cortisol to inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11-βHSD2) due to loss-of-function mutation of 11-βHSD2. This leads to accumulation of cortisol, which has mineralocorticoid activity, leading to the clinical triad of HTN, hypokalemia, and metabolic alkalosis. AME's clinical

manifestation is independent of renin and aldosterone. Of note, glycyrrhetinic acid from licorice inhibits 11-βHSD2. Individuals who habitually ingest a high amount of licorice may present similarly as AME, although to a milder degree. AME and licorice ingestion may be differentiated based on urine free cortisol-to-cortisone ratio. Urine free cortisol-to-cortisone ratio above 5 may be consistent with AME, while a lower ratio above 1 may be consistent with licorice ingestion. Review the evaluation of conditions associated with the triad of HTN, hypokalemia, and metabolic alkalosis (**Figure 2.16**).

85. **Answer:** B

Current metabolic alkalosis is not severe. Hypokalemia, however, is moderately low. The patient has been diuresing at a safe rate. Adding acetazolamide is not yet indicated.

As the patient can diurese well on a reasonable dose of diuretics, there is no need to start dialysis for UF or convert the current spot dosing of bumetanide to a continuous infusion.

Adding spironolactone can gently improve potassium, metabolic alkalosis, diuresis, as well as long-term cardiovascular outcome.

86. **Answer:** D

The change in color of bloodlines to deep red (also described as "port wine" color) and clinical manifestation of severe bradycardia suggest the presence of hemolysis where severe hyperkalemia can cause severe bradycardia/asystole. In the case of hemolysis, dialysis must be immediately stopped, bloodline clamped, and blood in circuit discarded.

β-Blocker poisoning alone does not cause hemolysis.

The ultrafilter/endotoxin filter is an optional process done at the final step of water treatment to remove any residual bacteria and endotoxins. Adding softeners is optional for areas with hard water. Defects or absence of ultrafilter/endotoxin and softeners steps should not cause hemolysis.

Carbon filtration removes chlorine and chloramine (added to municipal water) and organic contaminants. Chloramine can cause hemolysis. Carbon filtration is done prior to reverse osmosis

because chlorine and chloramine can damage the membrane used in reverse osmosis. Damage to the carbon filtration system is the most likely cause of hemolysis in this dialysis unit.

87. **Answer:** B

In this patient with distal RTA due to low mineralocorticoid activity, adding fludrocortisone would be appropriate. As adding fludrocortisone can cause sodium retention and worsen edema and HTN, adding concurrent furosemide is indicated. The use of furosemide also increases sodium delivery to collecting tubules where fludrocortisone works. Fludrocortisone works by increasing the reabsorption of sodium delivered to collecting tubules via the epithelial sodium channel, thereby optimizing potassium and hydrogen secretion.

Zirconium cyclosilicate (Lokelma) daily decreases potassium levels without directly treating the underlying cause of RTA type 4.

Low-sodium diet may reduce sodium delivery to collecting tubules and renders fludrocortisone ineffective.

Thiazide diuretic will unlikely improve the patient's edema.

88. **Answer:** B

This patient has a Bosniak class II cyst, which requires no follow-up. In addition, at age 96, any additional evaluation is questionable, given that the longevity of a patient is likely shorter than the time it takes for any suspicious lesion to become life-threatening/shortening.

Bosniak CT-based cyst classification

Class I:

- Cyst with hairline thin wall; no septation, calcification, or solid component; no enhancement with contrast CT
- Management: benign cyst, no follow-up required

Class II

- Type 1:
  - Cyst with a few hairline thin septations; fine calcification or short segment of slightly thickened calcifications may be seen in cyst wall or septae

    - Management: benign simple cyst, no follow-up required
- Type 2:
    - Uniformly high attenuation lesion less than 3 cm, well marginated, nonenhancing
    - Management: likely benign renal lesion, no follow-up required

Class IIF (F is for follow-up)

- Type 1: cysts with multiple hairline thin septa or minimally smooth thickening of wall or septa with or without subjective perceived enhancement (without measurable enhancement) with radiocontrast that may have thick or nodular calcifications
- Type 2: intrarenal nonenhancing hyperattenuating renal lesions greater than 3 cm
- Management of IIF
    - Most Bosniak IIF masses are benign. When malignant, most are indolent. Follow-up at 6 and 12 months, then annually for 5 years to assess for changes.
    - For kidney transplant recipients: ultrasound evaluation 4 times a year; CT or MRI scan yearly; nephrectomy if progressive lesions, even if not reaching category III/IV.

Class III

- Cystic masses with thickened irregular or smooth wall/septa with measurable enhancement. (Contrast enhancement implies vascularized mass, thus possible malignancy.)
- Management: Bosniak III masses have an intermediate probability of being malignant (cystic RCC and multiloculated cystic RCC). Other differential diagnoses include hemorrhagic cysts, chronically infected cysts, and multiloculated cystic nephroma. Consult urology.

Class IV

- All components of class III plus the presence of soft tissue components/nodules with measurable enhancement adjacent to and independent of cyst wall or septum

- Management: A large majority of Bosniak IV cystic renal masses are malignant. Consult urology.

For interested readers, a proposed detailed update of the current Bosniak classification is reviewed in Silverman et al, Bosniak Classification of Cystic Renal Masses, Version 2019.

89. **Answer:** B

The allograft biopsy shows an artery with endotheliitis diagnostic of acute T-cell mediated rejection (TCMR) grade IIA. The most appropriate treatment for Banff grade II A (aka vascular rejection) is ATG.

90. **Answer:** B

A urine osmolar load of 252 mOsm/kg × 4.2 L =1,058 mOsm is higher than expected for this patient's dietary intake (average American daily dietary intake is 10 mOsm/kg/d × body weight [= 60 kg for this patient] = 600 mOsm/d). The much higher urine solute load of 1,058 mOsm indicates an osmotic diuresis.

Since the urine osmolality is made up of predominantly sodium and potassium, that is, 2 × (75 + 27) ÷ 252 = 0.8 × 100% = 80%, the osmotic diuresis may be due to the ongoing saline infusion.

For a solute load of 1,058 mmol, a urine volume of 1,058/295 = 3.6 L of urine is expected. Since the actual urine volume is 4.2 L, 0.6 L is osmolar-free water. This osmolar-free water indicates that the patient also has a low degree of aquaresis. This could be due to free water intake in excess of solute and/or mild degree of defective tubular water reabsorption associated with urinary obstruction.

91. **Answer:** B

Synthetic cannabinoids can cause AIN. However, hypokalemia, not hypomagnesemia, has been reported to be associated with synthetic cannabinoid intoxication.

92. **Answer:** B

Secondary hyperaldosteronism from hypovolemia does not present with hypokalemia. In hypovolemia, there is no or very minimal sodium delivery to the epithelial sodium channel (ENaC)

at the collecting tubules for potassium exchange to occur. For this reason, serum potassium is typically not low in hypovolemia-induced hyperaldosteronism. Note, however, in acute vomiting where there is high urinary sodium delivered distally, renal potassium wasting can occur.

93. **Answer:** D
Cisplatin is associated with Fanconi syndrome and renal salt wasting. The latter can lead to severe hyponatremia and rapid volume depletion requiring high salt supplement. Renal salt wasting is evidenced as high urine volume with high urine sodium ± potassium concentrations. The presence of glucose in a patient with euglycemia and low-level proteinuria in the urine is consistent with Fanconi syndrome. Some patients may also present with proximal RTA due to proximal tubular bicarbonate wasting.

94. **Answer:** B
Rifampin is a potent CYP3A4 inducer and can cause subtherapeutic concentrations and treatment failure of various drugs including calcineurin inhibitors (CNIs) (CSA, tacrolimus), mTOR inhibitors (sirolimus, everolimus), and statins. Significant dose increase in affected drugs is generally required. Diltiazem is a moderate CYP3A4 inhibitor that is commonly used to boost CSA or tacrolimus levels. Therefore, stopping diltiazem can decrease tacrolimus level. However, it is unlikely that missing one dose of diltiazem would result in nearly undetectable tacrolimus level. Isoniazid and pyrazinamide are weak CYP3A inducers and are generally safe to use in patients receiving calcineurin inhibitors.

95. **Answer:** B
Metoprolol is dialyzable. The increase in BP and heart rate toward the end of dialysis treatment is likely due to the loss of metoprolol with dialysis.
Carvedilol is nondialyzable. Its use helps maintain stable intradialytic blood level and improve survival from cardiovascular complications.

Adding diltiazem or verapamil may help with this patient's problem at the expense of creating unnecessary polypharmacy. Patients with underlying ischemic heart disease are more likely to present with intradialytic hypotension rather than HTN.

Although increasing dialysate temperature may theoretically help lower intradialytic BP, it does not target the main problem of the loss of metoprolol during dialysis.

Review dialyzability of antihypertensive agents:

Nondialyzable (or low dialyzability) medications:

- First-line agents: amlodipine, ARB, ACEi (fosinopril, ramipril, benazepril)
- Others: MRAs, carvedilol, labetalol, hydralazine, α-blockers, clonidine

Dialyzable medications: atenolol, metoprolol, and ACEi (enalapril, lisinopril, and perindopril)

96. **Answer:** D

Since mechanical hyperventilation is required to maintain the patient's oxygenation, respiratory alkalosis is an obligated effect. Serum bicarbonate should be maintained at a level at which blood pH is as close to the physiologic range of 7.35 to 7.45 as possible. In this case, a serum bicarbonate of 15 mEq/L keeps the blood pH at 7.42. To maintain this serum bicarbonate level, a dialysate bicarbonate concentration should be in the lower range of 20 to 25 mEq/L. A high bicarbonate dialysate that normalizes serum bicarbonate to 24 mEq/L would bring the blood pH to 7.6, which can be highly arrhythmogenic.

97. **Answer:** A

The skin lesion described is consistent with calcific uremic arteriolopathy.

Based on the history and medication list, the current patient's risks include female gender, obesity, T2D, steroids, warfarin, calcitriol, and iron therapy.

Treatment is to reduce risks and discontinue any contributing medications. In this case, medications that may be discontinued include iron and, possibly, steroids. Since this patient needs

anticoagulation for atrial fibrillation, switching to a direct oral anticoagulant may be considered.

King BJ, El-Azhary RA, McEvoy MT, et al. Direct oral anticoagulant medications in calciphylaxis. *Int J Dermatol*. 2017;56(10):1065-1070.

Review potential therapy for calcific uremic arteriolopathy

- Avoid: warfarin, vitamin D analogs, calcium-based phosphate binders
- Supportive care: wound care (which may include treatment with hyperbaric oxygen), control of secondary hyperparathyroidism and hyperphosphatemia, use lower calcium dialysate (only if safely tolerated due to hypotension associated with lower calcium dialysate), debridement only when absolutely necessary due to increased risk of infections, consider bisphosphonate therapy and cinacalcet if clinically appropriate.
- IV sodium thiosulfate (STS) 25 g thrice weekly can be administered during the last 30 minutes of each HD session. Efficacy is variable and duration of therapy is undefined, but most reported cases required prolonged treatment of weeks to months. Side effects of STS include nausea, elevated anion gap metabolic acidosis (due to accumulation of lactic acidosis, thiosulfuric acid, and hydrogen sulfide), volume overload, QTc prolongation, and hypocalcemia.
- Optimize dialysis dose in dialysis-dependent individuals.
- Promising therapy under clinical investigation: SNF472 is an IV formulation of myoinositol hexaphosphate that can directly inhibit the formation of calcium and phosphorus crystals, thereby preventing ectopic calcium deposition.

98. **Answer:** A

The patient has normotensive SRC.

SRC occurs in 2% to 4% with limited disease (skin involvement *distal to* elbows and knees only) and 5% to 10% of diffuse scleroderma (skin involvement *proximal and distal to* elbows and

knees). SRC may present as a hypertensive or normotensive form.

Hypertensive SRC:

- SPB greater than 140 or DBP greater than 90 mm Hg, or a rise in SBP greater than 30 or DBP greater than 20 mm Hg from baseline, AND
- One of the following features: increase in SCr more than 50% from baseline or more than 120% of upper normal limit; proteinuria greater than 2+ by dipstick; hematuria greater than 2+ by dipstick or greater than 10 RBCs/HPF; thrombocytopenia less than 100,000 platelets/μL; hemolysis; or hypertensive encephalopathy

Normotensive SRC:

- Increase in SCr more than 50% above baseline or SCr more than 120% of upper normal limit, AND
- One of the following features: proteinuria 2+; hematuria greater than 2+ by dipstick or greater than 10 RBCs/HPF; thrombocytopenia less than 100,000 platelets/mL; hemolysis; renal biopsy with microangiopathy consistent with SRC; or hypertensive encephalopathy

The cornerstone in the management of SRC is the use of an ACEi.

99. **Answer:** B

This is a patient with a history of systemic scleroderma who presents with HTN and evidence of TMA, consistent with SRC. The patient has high risks for SRC, including recent high-dose GC therapy, pulmonary vasculopathy with pulmonary HTN, and preceding kidney injury. The cornerstone of SRC treatment is ACEi. Other agents (eg, CCBs) may be added as needed for BP control, but β-blockers are generally avoided, given concerns for potential reduction in cardiac output (even in patients without presenting HF) and vasospastic effects on the microcirculation. TMA may be present in 40% to 50% of SRC cases. The use of eculizumab may be considered in severe and refractory cases.

The use of endothelin receptor antagonist requires more data at the time of this writing.

Recall diagnostic criteria for hypertensive versus normotensive SRC:

Hypertensive SRC: SPB greater than 140 or DBP greater than 90 mm Hg, or a rise in SBP greater than 30 or DBP greater than 20 mm Hg from baseline, AND one or more of the following features: increase in SCr more than 50% from baseline or more than 120% of upper normal limit; proteinuria greater than 2+ by dipstick; hematuria greater than 2+ by dipstick or greater than 10 RBCs/HPF; thrombocytopenia less than 100,000 platelets/μL; hemolysis; or hypertensive encephalopathy

Normotensive SRC: increase in SCr more than 50% above baseline or SCr more than 120% of upper normal limit, AND one or more of the following features: proteinuria 2+; hematuria greater than 2+ by dipstick or greater than 10 RBCs/HPF; thrombocytopenia less than 100,000 platelets/μL; hemolysis; renal biopsy with microangiopathy consistent with SRC; or hypertensive encephalopathy

00. **Answer:** D

Recurrent Alport syndrome does not occur in the transplanted graft because the donor kidney has a normal glomerular basement membrane. The introduction of normal collagen in the basement membrane of the donor allograft may induce antibody formation to the donor kidney collagen, resulting in the developing de novo anti-GBM glomerulonephritis. X-linked females do not develop post-transplant anti-GBM because they generally carry a normal copy of the affected gene.

The biopsy shows interstitial inflammation and moderate tubulitis diagnostic for acute T-cell mediated rejection grade 1A. The most appropriate treatment for Banff grade 1A rejection is high-dose IV methylprednisolone.

01. **Answer:** B

The patient has no peripheral edema to mobilize with hyperoncotic 25% albumin. The infusion of 25% albumin in

intravascularly depleted patients who have no peripheral edema increases the risk of tubular injury. The increased oncotic pressure within peritubular capillaries reduces perfusion of oxygen and nutrients to renal tubules and can lead to tubular injury and necrosis. Mobilization of ascitic fluid into central venous volume with 25% albumin is very minimal and is thought to be less than 500 mL/d.

Packed RBCs are only used for severe anemia.

The lactate in lactated Ringer may not be metabolized by the cirrhotic liver well, which loses the intended benefit for using lactated Ringer. In addition, the low-sodium concentration in lactated Ringer may not be the best fluid to use in this patient with hyponatremia.

Normal saline is likely the best volume expander in this patient. In addition to being a good volume expander, it may slightly help improve the patient's current hyponatremia.

02. **Answer:** C

The mycophenolic acid derivatives (mycophenolate mofetil or mycophenolate sodium) should be discontinued in anticipation of pregnancy due to the increased risk of first-trimester pregnancy loss and congenital malformation. Similarly, mTOR inhibitors should be discontinued in anticipation of pregnancy. The use of mTOR in pregnancy has been shown to be associated with fetal mortality, decreased fetal weight, and delayed ossification of skeletal structure.

In contrast to the mycophenolic acid derivatives and the mTOR inhibitors, AZA use in pregnancy is generally safe.

03. **Answer:** B

Headaches, nausea, and vomiting may occur during dialysis treatments. Causes may include disequilibrium syndrome, large-volume removal (typically due to high interdialytic weight gain), intradialytic hypotension, acute fall in caffeine levels in patients with habitual high caffeine intake, rapid electrolyte changes (eg, sodium, glucose level), fluoride contaminants from water system, intradialytic increase in intraocular pressure (rare), and other

non–dialysis-related causes (subdural hematoma, psychological factors).

Dialyzer membrane composition and biocompatibility and temperature of dialysate are unlikely to contribute to the current patient's symptoms.

The use of mannitol is also likely noncontributory because this patient is a chronic dialysis patient. Disequilibrium syndrome is unlikely.

High interdialytic weight gain requiring large-volume removal and associated complications with intradialytic hypotension can contribute to this patient's current symptoms and should be reviewed.

04. **Answer:** C

Both thiazide and loop diuretics increase renal Mg^{2+} wasting. SGLT2i and amiloride decrease renal Mg^{2+} wasting and may provide added benefits to patients with hypomagnesemia.

05. **Answer:** A

Regarding kidney/skin biopsy in patients with AS:

Kidney biopsy: The classic kidney biopsy findings for AS include lamellation and/or basket weaving pattern of the GBM. These findings may not be present in early disease.

Recall the [α5, α5, α6] protomer is present in the skin, smooth muscle, esophagus, and kidneys.

Skin biopsy can be stained for α5(IV) chain. Skin does not have α3 or α4(IV) chain.

- Absent or segmental staining for α5(IV) chain suggests X-linked AS.
- Normal staining may signify:
  - Autosomal recessive or dominant AS involving the α3 or α4(IV) chain
  - Mutation of α5(IV) that affects the function, but not structure, of the chain.
  - Diseases other than AS

06. **Answer:** A

Indications for immediate removal of CVC (Lok, Charmaine E. et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am J Kidney Dis*. 2019;75(4):S1-S164)

- Tunnel infection
- Infection involving **S. aureus*, *Pseudomonas aeruginosa*, fungal or mycobacterial organisms
  *Of interest, catheter salvage in a significant proportion of patients in the context of *S. aureus* infection has been reported in observational studies.
- Severe sepsis and/or hemodynamic instability
- Metastatic infection
- Persistence of fever or bacteremia 48 to 72 hours after initiation of antibiotics to which the organism is susceptible.
  The current patient meets criteria for immediate CVC removal based on these criteria. CVC replacement should be delayed until blood cultures and fevers resolve.

Catheter salvage

- Attempt at salvage of the catheter may be attempted for infections involving coagulase negative *Staphylococcus* or gram-negative organisms if good response to treatment and no fever or bacteremia beyond 48 to 72 hours.
- Risk of recurrent bacteremia if the catheter is not removed has been shown to be reduced with the use of an antibiotic "lock."

Removal of CVC with replacement over a guidewire may be attempted if no purulence or other signs of infection at exit site or tunnel if exchanging over same site. For tunnel infections, if there is purulence or other signs of infection at exit site or tunnel, exchange may be possible over new noninvolved insertion site using the same side to preserve access.

07. **Answer:** D

The biopsy shows isometric vacuolization of proximal tubule cells, suggestive of acute calcineurin inhibitor (CNI) toxicity. CNI to belatacept conversion therapy may be considered in EBV-seropositive patients with biopsy-documented CNI toxicity or CNI-

induced thrombotic microangiopathy and absence of acute rejection (FDA black box warning: belatacept is contraindicated in EBV-naïve kidney transplant recipients or in those with unknown EBV serostatus due to increased risk of post-transplantation lymphoproliferative disorder (PTLD) predominantly involving the central nervous system). Although mTOR inhibitor is nonnephrotoxic, its use is not recommended in patients with proteinuria.

08. **Answer:** D

2,8-DHA stone

Adenine phosphoribosyltransferase (APRT) enzyme deficiency is a rare autosomal recessive disorder of purine metabolism that leads to kidney stones and CKD. APRT deficiency prevents adenine recycling (from the purine nucleotide salvage pathway) and leads to adenine accumulation. Xanthine oxidase metabolizes the accumulated adenine to 2,8-DHA, which is insoluble in the urine and can cause kidney injury with or without stone formation. 2,8-DHA stone is radiolucent, which may be mistaken for uric acid stone. In terms of treatment, low-dose allopurinol or febuxostat with uptitration as needed for disappearance of 2,8-DHA crystals in the urine sediment has been suggested. Optimal dosing has not been defined.

09. **Answer:** A

African American living donor candidates with risk factors for the development of ESKD such as young age (<44 years), male gender, history of smoking, obesity (body mass index >30 kg/m^2), HTN, low normal eGFR (90-99 mL/min/1.73 m^2), and a family history of ESKD, HTN, or diabetes in a first-degree relative may be considered for APOL1 genetic testing. To protect the donor's privacy, the transplant team may not reveal the donor candidate's APOL1 genotype to the recipient.

10. **Answer:** D

Diarrhea/enterocolitis may lead to reduced intestinal P-glycoprotein activity and significantly increase blood levels of drugs that are substrates of P-glycoproteins. Patients receiving

tacrolimus, a P-glycoprotein substrate, can present with toxic levels during episodes of diarrhea or enterocolitis. This does not occur with CSA because CSA is a potent P-glycoprotein inhibitor in gut enterocytes.

Fluconazole and all "azole" antifungals are moderate-to-strong CYP3A4 inhibitors. The concomitant use of fluconazole and calcineurin inhibitor (CSA or tacrolimus) can lead to markedly elevated CNI levels. In patients receiving CSA or tacrolimus, great care must be taken when starting and stopping these drugs.

Clarithromycin use can also increase calcineurin inhibitor level via inhibition of CYP3A4 activity.

11. **Answer:** B

    The patient has significant hyperkalemia. The most important consideration is the presence of ECG changes associated with hyperkalemia (ie, peaked T waves, widened QRS). Obtaining an ECG should be the first step in managing hyperkalemia. In the meantime, a repeat chemistry may be sent to the laboratory for confirmation. This patient should not be alkalinized, given severely low serum calcium. Alkalinization reduces ionized calcium levels and can lead to life-threatening arrhythmias and neurologic complications. Insulin and 50% dextrose may be administered if hyperkalemia is confirmed.

12. **Answer:** B

    This is a young patient with relatively good residual kidney function with a busy day schedule who is starting PD. Initial therapy should be low (low number of dwells, low volume) and uptitrated as needed and as tolerated. Given her busy daytime schedule, nighttime APD is likely the best fit for her. Starting PD at high volume and high frequency of exchanges can be emotionally "traumatizing" for patients and may cause early burnout. In addition, initial high dwell volumes can increase the risk of leakage. Maximizing strategies to minimize potential complications at the start of PD is warranted to ensure long-term adherence.

13. **Answer:** C

This acutely ill patient has profuse watery diarrhea with severe hypokalemia. Secretory diarrhea with associated potassium wasting should be considered, such as Ogilvie syndrome. Ogilvie syndrome is a condition thought to result from an imbalance of sympathetic and parasympathetic input in the distal colon that may be seen in patients with acute illness. The diagnosis can be easily made with an abdominal radiograph (x-ray), which will show marked colonic distension. The diarrhea is driven by potassium secretion, with potassium loss exceeding 100 mmol daily, presumably via colonic upregulation of BK potassium channel. Risk factors for Ogilvie may include advanced age, trauma, severe infection, major surgical procedures, and admissions for cardiovascular diseases.

Unlike Ogilvie syndrome, common forms of diarrhea are due to inhibition of sodium reabsorption or chloride secretion. Diarrhea associated with *C. difficile* is commonly associated with significant leukocytosis, which is absent in the current patient. In addition, NAAT for *C. difficile* toxin gene is negative.

Antibiotic-induced diarrhea is typically not severe enough to cause severe hypokalemia in just a few days.

The patient has no history of liver and pancreatic disease. Liver function tests and lipase are within normal range. Pancreatic insufficiency is less likely. A trial of pancrelipase will likely not be helpful.

Sunnoqrot N, Reilly RF. Hypokalemia associated with colonic pseudo-obstruction (Ogilvie's syndrome). *Case Rep Nephrol Dail*. 2015;5:118-123.

Conner S, Nassereddin A, Mitchell C. Ogilvie syndrome. In: StatPearls [Internet]. StatPearls Publishing; 2024.

14. **Answer:** C

Genetic inheritance/predisposition to FSGS

A large number of autosomal dominant and recessive genes inherited with variable penetrance have been identified that can cause FSGS. Genetic testing may be beneficial for some individuals, predominantly to avoid glucocorticoid (GC), as most

are steroid resistant. Mutations in phospholipase C ε1 (PLCε1) may be an exception.
Genetic FSGS may have minimal to more than 80% foot process effacement depending on the location and function of the affected gene.
Inheritance of two polymorphic risk alleles (G1, G2) of the *APOL1* gene increases the risk of FSGS, as well as the risk of progressive functional decline in patients with nondiabetic kidney diseases. These polymorphisms are more common in individuals of more recent African ancestry. APOL1 polymorphisms protect against *Trypanosoma brucei*, a parasite spread by tsetse flies in Africa.
Missense APOL1 polymorphisms predispose patients to an excess risk of ESKD.
The presence of APOL1 risk polymorphisms is not a contraindication for a trial of GC therapy.

15. **Answer:** A
This patient without any cardiac history continues to be volume overloaded despite being on a high dose of PD and dietary restriction and relatively high-dose diuretics. Possible underlying problems include obstructed catheter tip, diaphragmatic leak or leakage to other body compartments, fibrin plug of tubing, intra-abdominal pathology, severe constipation, or peritoneal membrane failure.
To diagnose membrane failure, a trial of 4.25% dextrose exchange may be performed.
Review UF failure
Common causes of volume overload in a PD patient
Non-PD procedure-related causes: loss of residual kidney function, congestive HF, dietary noncompliance, PD nonadherence
PD procedure-related causes:
    - Mechanical problems (migration, kinking of catheter), constipation affecting dialysate flow, fibrin plug (fibrin may be seen in drainage bags), dialysate leaks to other body cavities, and peritoneal membrane failure. In the case of fibrin plugs, irrigate tubing system and add heparin to dialysate bags.

- Poorly controlled diabetes, such as blood glucose greater than 250 mg/dL, dissipates the osmotic gradient necessary for optimal UF.
- Increased lymphatic reabsorption associated with increased intra-abdominal pressure: sitting position is worse than standing and lying positions.
- Intra-abdominal pathology

Diagnosing peritoneal membrane failure
Peritoneal membrane failure may be diagnosed as follows:

- Inability to maintain euvolemia despite use of greater than 3 hypertonic dialysate solutions per day, or
- Failure to ultrafilter greater than 400 mL with a 4.25% solution over 4 hours (rule of 4s)
- Peritoneal equilibration testing reveals high Dialysate/Plasma creatinine ratio (D/P creatinine) of creatinine (ie, >0.8).

Causes of peritoneal membrane failure

- Early: acute inflammation
- Late: alterations in peritoneal membrane (eg, thickening, fibrosis)

16. **Answer:** A
    The patient's serum uric acid is within normal limit. There is no need for febuxostat or allopurinol. Urine uric acid is at the upper limit of normal, but still within acceptable range. The best preventive step against further uric acid stone growth is alkalinization of the urine because uric acid precipitates at low urine pH. The goal is to bring the urine pH to greater than 6.0, with care not to over-alkalinize where calcium carbonate stones (calcium apatite, brushite) can precipitate at high urine pH. Potassium citrate can be used for this purpose. Spacing out the agent over the day is preferred because urine pH varies over the day. Any time period when urine pH is low, uric acid may crystallize to form stones.
17. **Answer:** A

The patient described has IgG4-RD.

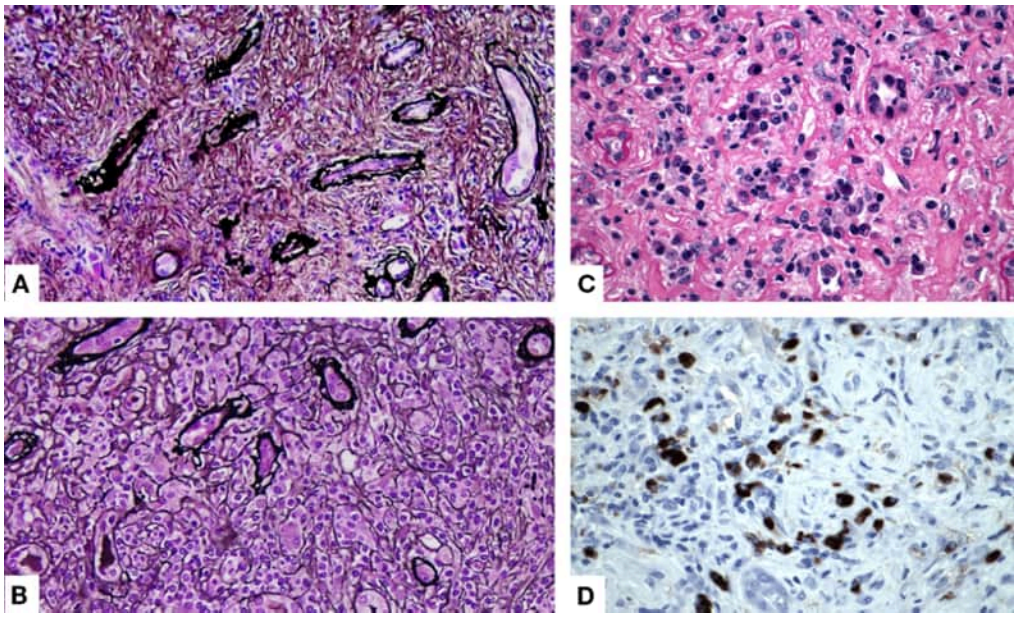
IgG4-RD is thought to be due to an inflammatory immune response triggered by an autoimmune process or the presence of an infectious agent. The influx of inflammatory cells leads to multiorgan enlargement, cytokine release, eosinophilia, elevated IgG4 and IgE levels, and fibrosis of affected organs. Lymphoplasmacytic infiltration can lead to the formation of mass lesions in various organs, including pancreas, autoimmune pancreatitis, enlarged (submandibular) salivary glands, kidneys (tubulointerstitial nephritis), lungs, lymph nodes, meninges, aorta (chronic sclerosing aortitis and periaortitis), breast, prostate, thyroid (thyroiditis), pericardium, skin, and even bone (destructive lesions resembling granulomatous polyangiitis).

Renal involvement in patients with IgG4-RD may include tubulointerstitial nephritis, membranous GN, IgG4 plasma cell arteritis, and obstructive uropathy from retroperitoneal encasement/fibrosis.

Given the low level of proteinuria with minimal albuminuria, tubulointerstitial disease is the most likely associated kidney lesion for the current patient.

Myeloma kidney is unlikely, given negative serum and urine protein immunofixation and negative serum κ/λ.

Kidney biopsy of a patient with IgG4-RD involving the kidneys may reveal dense lymphoplasmacytic infiltrates consisting of lymphocytes, plasma cells, and eosinophils. The interstitial fibrosis typically has a "storiform" pattern, with a whorled pattern of fibrosis around mononuclear cell infiltrates with or without eosinophils. Individual inflammatory cells may be encased in fibrosis ("bird's-eye pattern"). Seeing greater than 10 IgG4+ plasma cells in one 40× field or a ratio of greater than 50% of IgG4+ to IgG4 - plasma cells is highly suggestive of IgG4-RD.



IgG4-RD. A. There is interstitial fibrosis in a storiform (whirling) pattern with tubular atrophy and interstitial inflammation (periodic acid methenamine silver × 200). B. Fibrosis surrounding individual and small clusters of inflammatory cells ("bird's-eye" fibrosis) (periodic acid methenamine silver × 200). C. Small aggregates of lymphocytes and plasma cells (hematoxylin and eosin × 400). D. IgG4 immunohistochemical stain showing positive staining in more than 50% of the plasma cells and in greater than 10 plasma cells in one 40× field (×400).

18. **Answer:** A

Streptococcal peritonitis may present with severe abdominal pain. The diagnosis of peritonitis must meet at least two out of three criteria:

- Clinical signs consistent with peritonitis such as abdominal pain and/or cloudy effluent
- PD cell count with greater than 100 WBCs/μL or with more than 50% PMN in differential count (>50% PMN is likely a better indicator for peritonitis than having >100 WBCs/μL). False negatives may be seen if cell count is obtained early in the course of peritonitis or during short dwell (*collect fluid after at least 2-hour dwell time*).
- Identification of infective organism(s) from the dialysis effluent via Gram stain or culture

Note that 15% to 40% of PD fluid cultures are negative in clinical peritonitis. Negative cultures may be caused by recent antibiotic exposure, suboptimal sample collection or culture method, or infection with an atypical organism (such as fungi, *Mycobacterium*, *Campylobacter*, *Ureaplasma* sp., *Mycoplasma*, or enteroviruses).

19. **Answer:** A

    In addition to the diuretic effect, thiazide and loop diuretics also have vasodilatory effects. This partially explains the reason for the use of thiazide diuretics as an antihypertensive agent.

    Thiazide diuretics can increase calcium reabsorption, which may provide a beneficial effect in patients at risk for osteoporosis.

    Since thiazide diuretics have long half-lives (eg, metolazone's half-life is 6-8 hours), they do not necessarily have to be given 30 minutes prior to the administration of loop diuretics for synergistic diuresis.

    The use of SGLT2i is associated with uricosuria, which may be beneficial to patients with gout.

20. **Answer:** B

    Recall the basic arterial layers starting from outside the lumen: adventitia > media > intima. Concentric calcifications can lead to arterial stiffening.

    Medial artery calcification (MAC) is associated with better survival compared with those with intimal calcifications (seen with classic coronary artery disease risks), but worse survival compared to those with no calcification.

    The use of denosumab may be beneficial in reversing/treating vascular calcifications. More data are needed.

21. **Answer:** D

    Checkpoint inhibitors including anti–PD-1 antibody and anti–CTLA-4 antibody have been reported to precipitate AIN with or without glomerular lesions such as MCD, MN, FSGS, and TMA. The severe proteinuria suggests severe podocytopathy (which may present as MCD on light microscopy), and the glucosuria suggests tubular injury, such as AIN.

22. **Answer:** B

    TMA associated with acute AMR is generally limited to the kidneys. aHUS has a very high risk of recurrence in patients with mutations involving circulating factors (particularly complement factors H and I). Normal ADAMTS13 activity rules out TTP.

23. **Answer:** D

    UPN is a distal symmetric sensorimotor polyneuropathy that typically affects lower limbs but may spread to upper limbs. UPN is characterized by demyelination of large nerve fibers leading to axonal degeneration. UPN occurs in 60% to 100% of patients with CKD and ESKD and may be more common in males.

    Possible contributing factors include deficiencies in thiamine, zinc, and biotin and decreased transketolase activity; accumulation of phenols, myoinositol, β2-microglobulin, and other uremic "middle-molecular-weight molecules"; and others including hPTH and electrolyte disturbances, particularly dyskalemias.

    Patients affected with UPN may be asymptomatic until GFR is less than 15%. Both slowly and rapidly progressive diseases may occur, the latter in association with acute illnesses such as sepsis. Typically, patients may present with a slowly progressive sensorimotor axonal neuropathy, which advances proximally, starting from lower limbs with possible spread to upper limbs; paresthesia, numbness, hyperesthesia to noxious stimuli, thermal sensitivity impairment, RLS, cramps, impaired deep tendon reflexes, weakness, imbalance, lower limb atrophy, and optic neuritis (sudden vision deterioration, blurry vision).

    In contrast to UPN, diabetic neuropathy is a slowly and progressive condition that is primarily associated with sensory deficit in a "stock-and-glove" distribution.

    Patients with severe B_{12} deficiency may present with similar neurologic findings as UPN. However, B_{12} deficiency is also associated with cognitive slowing, dementia, psychosis, and macrocytic anemia. The current patient does not have macrocytic anemia or any cognitive impairment. Of side note, chronic

metformin use (eg, >2 years) in patients with DM may be associated with B_{12} deficiency.

RLS is characterized as an unpleasant sensation in lower extremities with the compulsive need to move the legs, is worse in the evening, and improves with walking. RLS is not associated with muscle weakness and autonomic dysfunction.

24. **Answer:** A

This patient is at a very high risk with life-threatening thrombotic complications associated with NS. He received lisinopril and one dose of RTX with worsening proteinuria, hypoalbuminemia, and renal function. He should be treated with cyclophosphamide and GCs.

Rovin, Brad H. et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 100(4):S1-S276.2.

25. **Answer:** C

In general, volume overload is thought to delay the diagnosis of AKI and has been shown to be associated with worse outcome.

Program to Improve Care in Acute Renal Disease (PICARD) trial:

Fluid overload was associated with higher mortality at 60 days and hospital discharge.

Fluid overload at the time of AKI diagnosis or at peak SCr was NOT associated with favorable for renal recovery.

Finland AKI (FINNAKI) trial: Patients with fluid overload at KRT initiation had an increased risk of 90-day morality after adjusting for disease severity, time of KRT initiation, modality, and sepsis compared to those without.

Intensive Care over Nations study: Higher cumulative fluid administered over the first 72 hours, but not the first 24 hours, in critically ill patients was associated with increased hazard of death.

26. **Answer:** B

Patients with MN should be evaluated for associated conditions, independent of the presence or absence of anti-PLA2R antibodies or anti-THSD7A antibodies. Many centers will perform chest x-ray

or CT scan, look for iron deficiency, and require the patients to participate in the national screening program for breast and colon cancer; a prostate-specific antigen (PSA) test is done in adult males aged greater than 50 to 60 years. Rovin, Brad H. et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 100(4):S1-S276.

Urinalysis is only notable for proteinuria. It is unlikely that patient has any active glomerulonephritis such as ANCA vasculitis and antiglomerular basement membrane disease.

27. **Answer:** C

An increase in the ratio of total calcium: ionized calcium greater than 2.5 (when both are measured in mmol/L) or 10 (when the total is measured in mg/dL and the ionized is measured in mmol/L) is most suggestive of citrate accumulation. Here the ratio of total calcium to free calcium is 2.6 mmol/L/0.975 mmol/L = 2.7.

An elevated serum lactate greater than 4 mmol/L at initiation of CKRT or impaired "lactate clearance" in patients with serum lactate greater than 4 mmol/L has been associated with citrate accumulation. This patient's lactic acid level was initially 6 mmol/L and is increasing.

Incorrect Answers:

Option A is incorrect. The corrected calcium for serum albumin formula is used to correct the serum calcium in the setting of hypoalbuminemia. Using the corrected serum calcium to calculate the ratio of total calcium to free calcium has not been shown to be more predictive of citrate accumulation than the uncorrected ratio.

Option B is incorrect. An additional laboratory finding that supports citrate toxicity is an increasing AG due to the accumulation of negatively charged citrate. A worsening metabolic acidosis in itself is not predictive of citrate accumulation.

Option D is incorrect. A decreasing systemic ionized calcium level with an escalating rate of calcium infusion can be suggestive of citrate accumulation in the setting of an increase in the total

calcium: ionized calcium ratio but not a low systemic ionized calcium level by itself.

28. **Answer:** D

Calcium phosphate stone precipitates at high pH (ie, >6-6.5).

Struvite or triple phosphate stone is composed of magnesium ammonium phosphate and calcium carbonate apatite. The reason for the name "triple phosphate" is because phosphate is present in its trivalent form and combines with three cations, namely, NH_4^+, Mg^{2+}, and Ca^{2+}. The risk of struvite stone is recurrent urinary infection with urea-splitting organisms (urease-producing organisms), including *Proteus*, *Haemophilus*, *Yersinia*, *Klebsiella*, *Serratia*, *Citrobacter*, *S. epidermidis*, *Ureaplasma urealyticum*, and *Pseudomonas*. In the presence of the enzyme urease, urea is split into NH_3, which serves to buffer free H^+ from the urine causing the urine pH to be high. Together with Mg^{2+} and Ca^{2+}, NH_4^+ binds to phosphate in the urine to form triple phosphate stone. Bicarbonate in the urine per se cannot cause the formation of struvite stone without the excess NH_3 produced by urea-splitting organisms.

K citrate is preferred to Na citrate as an alkalinizing agent against stone formation. Sodium bicarbonate increases urine sodium excretion and associated urine calcium excretion, whereas K citrate increases urinary K excretion and reduces urine calcium excretion.

It is believed that calcium oxalate supersaturation is independent of urine pH.

29. **Answer:** B

Prednisone, tacrolimus, and venlafaxine may all contribute to his HTN. Based on the serum chemistry showing concurrent metabolic acidosis and hyperkalemia, tacrolimus is the most likely culprit. calcineurin inhibitors (CNI) have been implicated in causing HTN via the increased expression of sodium chloride cotransporters in distal convoluted tubules. The increased sodium reabsorption leads to HTN. Reduced sodium delivery to epithelial sodium channels in collecting tubules and secondary suppression

of renin-angiotensin system can lead to both hyperkalemia and metabolic acidosis. The preferred treatment of CNI-induced HTN has been suggested to be a thiazide diuretic.

30. **Answer:** C

ABD is characterized by low rates of bone formation and resorption, which may be evidenced by low tetracycline uptake. ABD may be associated with ectopic calcification and is the most common bone disorder observed in patients receiving PD.

Risks for ABD include:

- Oversuppression of PTH with calcitriol, calcimimetics, chronic exposure to high calcium (eg, calcium-containing phosphate binders, high calcium dialysate)
- Resistance to PTH, parathyroidectomy
- Advanced age
- DM
- Aluminum deposition (aluminum-based phosphate binders used in the past)

Laboratory studies associated with ABD:

- High bone-specific alkaline phosphatase suggests high turnover bone disease, thus rules out ABD.
- Relatively low/normal serum intact PTH level
- Hypercalcemia (serum calcium is not taken up by bone due to low bone formation)
- Normal to low serum phosphorus (due to low bone resorption)

31. **Answer:** A

Perinephric compression of a kidney, known as "Page" kidney (eg, large capsular hematoma, perinephric fibrosis), can present with HTN presumably due to reduced renal perfusion with compensatory activation of the renin-angiotensin and sympathetic nervous systems.

32. **Answer:** D

All medications listed can treat frequent relapsing MCD (MCD). However, every medication has different side effects.

Cyclophosphamide can effectively treat relapsing MCD. It has many side effects including sterility. This patient plans to have a family and have children, so it is not the best option for this patient.

Tacrolimus can worsen his glucose level. It is not the right choice. The patient has gained weight with prednisone, he does not like any additional medications that would affect his appearance, and CSA can cause gingival hyperplasia and hirsutism.

Mycophenolate can potentially worsen his bloating symptoms. Therefore, RTX would be the best choice.

Rovin, Brad H. et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 100(4):S1-S276.

33. **Answer:** C

Dose = Effluent rate/Patient weight = 1,800 + 1,000 + 200 + 250/100 kg = 32.5 mL/kg/h

34. **Answer:** B

This patient's laboratory findings suggest advanced CKD or ESKD. Therefore, allograft biopsy is not indicated. Currently, there is no consensus on the timing of dialysis reinitiation after a failed transplant. In general, dialysis reinitiation should be based on traditional clinical and/or laboratory parameters and the patient's overall wellness (or lack thereof).

In the present case, the patient most likely suffers from ESKD and symptomatic uremia; therefore, it would be appropriate to reinitiate dialysis. The clinical presentation of allograft pain and swelling in the setting of ESKD, as well as fever with negative infectious workup, suggests graft intolerance syndrome. The latter may respond to temporary intensification of immunosuppression, usually in the form of IV corticosteroid pulse. Both graft intolerance syndrome and infectious complications can present with fever. Therefore, high-dose corticosteroid should not be given until after infectious workup is negative.

35. **Answer:** B

Continuation of hydroxychloroquine reduces SLE flare during pregnancy. There are no data to suggest SGLT2i reduces the risk of preeclampsia. Of note, human data from a pharmaceutical database of inadvertent pregnancies during SGLT2i use revealed an increased incidence in miscarriages and congenital malformations (Muller DRP, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. *Front Endocrinol (Lausanne)*. 2023;14:1215356.). Thiazide diuretic may help control her BP, but not directly reduces the risk of preeclampsia. This patient appears to have chronic HTN as she presents with HTN prior to 20 weeks of gestational age. Her risks for preeclampsia include chronic stage 2 HTN, SLE, and body mass index greater than 30 kg/m^2. The best preventive measure is the use of low-dose aspirin to be started prior to 16 weeks until delivery. Review risks and preventive measures for preeclampsia below.

Risks for preeclampsia

- High risks: prior preeclampsia, chronic stage 2 HTN, pregestational DM, CKD, SLE, antiphospholipid antibody syndrome, multifetal pregnancy, assisted reproductive therapy for current pregnancy
- Moderate risks: prepregnancy body mass index greater than 30 kg/m^2, prior placental abruption, prior stillbirth, prior fetal growth restriction, maternal age above 35 years, family history of preeclampsia/eclampsia (PE/E), race (Black), nulliparity, history of adverse pregnancy outcome, low socioeconomic status
- Online Fetal Medicine Foundation preeclampsia risk calculator http://www.fetalmedicine.org/research/assess/preeclampsia/first-trimester

Preventive measures

- For women with high risk for PE/E, initiate low-dose aspirin prior to 16 weeks, and continue until delivery. Alternatively, some experts suggest discontinuation of aspirin by 36-week

gestation or 5 to 10 days prior to delivery to reduce bleeding complications.

- Other recommended preventive measures against PE/E include prepregnancy weight loss for individuals who are obese, moderate-intensity exercise 140 min/wk or more, daily calcium intake 1,000 mg/d (supplement with elemental calcium to achieve goal)
- Not recommended: high-dose folic acid, vitamin C, and vitamin E
- Insufficient data: metformin, statin

36. **Answer:** C

Tolvaptan was approved for use in adult patients with ADPKD by the FDA in 2018.

- Patients who most likely benefit from tolvaptan may be identified as having all of the following:
  - High risk of disease progression, identified as having ADPKD Mayo Class 1C, 1D, or 1E. The ADPKD Mayo Classification is based on kidney volume measurements (from CT without contrast or MRI without gadolinium), age, gender, race, height, and GFR.
  - eGFR 25 mL/min/1.73 m^2 or more, and
  - Age: 18 to 55 years old
- Patients with ADPKD Mayo Class 2 disease are only managed with conservative therapy. Mayo Class 2 refers to atypical presentations (eg, unilateral or segmental/asymmetric disease or bilateral disease with parenchymal atrophy).

The Mayo classification calculator may be found at: http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754 (Accessed December 14, 2024). The frequency of ESKD at 10 years increases from subclass 1A to 1E. In the younger CRISP cohort (age 15-46 years), the rate of ESKD at 10 years was 2.2% and 22.3% for those categorized as 1C and 1E, respectively. In the older Mayo cohort (age 15-80 years), the

rate of ESKD at 10 years was 2.4% and 66.9% for patients categorized as 1A and 1E respectively.

37. **Answer:** A

Serum K of 6 mEq/L × effluent rate 1 L/h = 6 mEq K removed per hour.

However, RF contains K 2 mEq/L, so the patient will receive 2 mEq K per hour (2 mEq/L K × effluent rate 1 L/h). Therefore, the net removal of K will be 4 mEq/h (6 – 2 = 4).

If we increased the effluent dose to 35 mL/kg/h or 1.75 L/h, the amount of K removed would be (serum K 6 mEq/L – effluent K 2 mEq/L) × 1.75 L/h = 7 mEq/h.

The difference would then be 7 mEq/h – 4 mEq/h = 3 mEq/h.

38. **Answer:** D

The current patient likely has primary hPTH. Patients with secondary hPTH are expected to have high levels of phosphorus, not low as seen in this patient.

This patient likely has high bone turnover disease with elevated alkaline phosphatase. Bone-specific alkaline phosphatase may be checked to differentiate between high bone turnover versus liver pathology.

Referral to otolaryngology is not yet indicated. Imaging study needs to be performed first.

Prescribing a calcium-sensing receptor agonist is not suggested in patients with advanced pre-dialysis CKD, given the lack of safety data.

39. **Answer:** C

This patient meets the criteria (bolded below) for polyarteritis nodosa (PAN) pending confirmation with angiography. HTN is common in patients with PAN. Early recognition is vital as multiorgan ischemia and infarction with delayed diagnosis can prove fatal.

Recall the American College of Rheumatology criteria for the diagnosis of PAN:

Having a radiographic or **pathologic diagnosis of vasculitis** and three or more of the following:

1. **Weight loss 4 kg or larger**
2. Livedo reticularis
3. Testicular tenderness
4. **Myalgia or leg weakness/tenderness**
5. **Mononeuropathy or polyneuropathy**
6. **DBP greater than 90 mm Hg**
7. **Elevated BUN or SCr unrelated to dehydration or obstruction**
8. Hepatitis B surface antigen (HBsAg) or hepatitis B surface antibody (HBsAb)
9. Arteriogram with aneurysms or occlusions of visceral arteries
10. **Positive PMN in small-/medium-sized artery (skin biopsy)**

Note that PAN is not associated with ANCA.

For the figures shown, A. Renal artery stenosis, B. fibromuscular dysplasia, C. PAN. Renal artery stenosis typically occurs within 2 cm from the aorta. Fibromuscular dysplasia typically occurs at the distal half to third of the renal artery. PAN occurs within the kidneys.

40. **Answer:** B

Kidney-alone transplantation is acceptable with HCV treatment in patients with *minimal to moderate chronic fibrosis* (stages I-III) or *compensated* liver cirrhosis (absence or mild portal HTN with hepatic portal venous gradient <10 mm Hg). Consultation with hepatology is recommended.

Patients with *decompensated* liver disease should be referred for simultaneous liver-kidney transplantation.